11.12.90

tober 1989 Vol 62 No 4

British Heart Journal

acM

25

monthly journal of cardiology
ublished in association with
he British Cardiac Society

Cuk-H06010-25-P25740

Protective effect of collateral vessels during coronary angioplasty *M S Norell, J P Lyons, J E Gardener, C A Layton, R Balcon* **241**

Impairment of diastolic function by shortened filling period in severe left ventricular disease *K S K Ng, D G Gibson* **246**

Influence of respiratory variations on right ventricular function *J L Caplin, W D Flatman, L Dyke, M N Wiseman, D S Dymond* **253**

Diagnosis of ventricular septal rupture after myocardial infarction: value of colour flow mapping *J Smyllie, K Dawkins, N Conway, G R Sutherland* **260**

Patterns of coronary artery disease in post-infarction ventricular septal rupture *J D Skehan, C Carey, M S Norrell, M de Belder, R Balcon, P G Mills* **268**

Cigarette smoking and non-fatal myocardial infarction in women: is the relation independent of coronary artery disease? *D S Freedman, H W Gruchow, J A Walker, S J Jacobsen, A J Anderson, K A Sobocinski, J J Barboriak* **273**

Superior QRS axis in ventricular septal defect *N J Shaw, M J Godman, A Hayes, G R Sutherland* **281**

Doppler flow characteristics in the assessment of pulmonary artery pressure in ductus arteriosus *A B Houston, M K Lim, W B Doig, J Gnanapragasam, E N Coleman, M P G Jamieson, J C S Pollock* **284**

Cross sectional echocardiographic anatomy of common atrioventricular valve in atrial isomerism *J Arisawa, S Morimoto, J Ikezoe, S Hamada, T Kozuka, T Sano, M Ogawa, H Matsuda, Y Kawashima* **291**

Quantitative effects of speckle reduction on cross sectional echocardiographic images *R J Massay, R B Logan-Sinclair, J C Bamber, D G Gibson* **298**

Magnetic resonance imaging at a high field strength of ventricular septal defects in infants *E J Baker, V Ayton, M A Smith, J M Parsons, E J Ladusans, R H Anderson, M N Maisey, M Tynan, N L K Fagg, P B Deverall* **305**

Dilatation with progressively larger balloons for severe stenosis of the pulmonary valve presenting in the late neonatal period and early infancy *S A Qureshi, E J Ladusans, R P Martin* **311**

The natural course of supravalvar aortic stenosis and peripheral pulmonary artery stenosis in Williams's syndrome *N G Giddins, J P Finley, M A Nanton, D L Roy* **315**

Family studies of congenital heart block associated with Ro antibody *W M H Behan, P O Behan, J M Reid, W Doig, J Gairns* **320**

British cardiology
Crisis in cardiovascular research in Britain *M F Oliver* **325**

Notices **328**

Correction: Right ventricular infarction: diagnostic accuracy of electrocardiographic right chest leads V3R to V7R investigated prospectively in 43 consecutive fatal cases from a coronary care unit *H R Andersen, E Falk, D Nielsen* **328**

CALCUTTA UNIVERSITY CENTRAL LIBRARY

British Medical Association

ASTM CODEN: BHJUAV 62(4) 241–328 (1989)

British Heart Journal

P, 25, 740

EDITOR Dennis Krikler ASSISTANT EDITORS M J Davies, Kim Fox, Peter Mills

EDITORIAL COMMITTEE
Clive P Aber Kate Bull Keith Dawkins Alan B Houston Barry R Keeton Michael Marmot
Alexander L Muir Paul J Oldershaw Philip A Poole-Wilson David B Shaw
Tom Treasure David E Ward John Watkins Peter Wilde
Editor: *British Medical Journal* Editor: *Cardiovascular Research*

TECHNICAL EDITOR Jane Dawson EDITORIAL ASSISTANT Anne Oliver
STATISTICAL ADVISER Stephen J W Evans

Notice to contributors

Papers relating to the heart and circulation should be sent in triplicate to the Editor, British Heart Journal, BMA House, Tavistock Square, London WC1H 9JR, and be prepared according to the *Uniform requirements for manuscripts submitted to biomedical journals* (Vancouver agreement) (*Br Med J* 1988;**296**:401–5). Authors are asked to complete a copy of the checklist provided (1989;**61**:131–2 (January issue)) when submitting their manuscripts for publication. The reference number given on the acknowledgement postcard sent out by the editorial office should be quoted on all subsequent correspondence and telephone inquiries. A covering letter must be signed by all authors stating that they have seen and approved the paper and that the work has not been, and will not be, published elsewhere. All authors will be required to transfer copyright of their articles to the journal before publication. (All material for possible publication (including Letters to the Editor) *must* be typed in *double spacing* with 4 cm margins.)

Ethical standards
Authors are expected to comply with the code of ethics known as the Declaration of Helsinki. Where appropriate, manuscripts should include a statement that the research protocol has been approved by the locally appointed ethics committee and that the informed consent of the subjects has been obtained.

Case reports should convey only the essential facts of a case and the discussion and bibliography be kept to a minimum. They should have no more than three authors, should not exceed 1500 words, and include no more than two Figures.

Abbreviations should *not* be used in the text, except for mathematical calculations and units of measurement.

References must be cited precisely according to the Vancouver agreement and be typed in *double spacing*. As a general rule, no more than three references should be cited for any one statement.

Authors are responsible for the accuracy of any references cited: these should be checked at source or with the listing in Index Medicus.

Units of measurement
All haematological and clinical chemistry measurements should be given as SI units. Blood pressures should be given in mm Hg. Measurements of length, height, weight, and volume should be reported in metric units and temperatures should be reported in degrees Celsius.

Tables must be typed on separate sheets and not in the text. Titles should be provided, and all abbreviations used must be given in full in a footnote.

Illustrations (for general requirements, please refer to *Br Heart J* 1984; **51:** 1–6).

Electrocardiograms: Black and white prints only should be sent and not the original tracings. If several tracings are grouped in a single Figure only a few complexes should be shown; the width should not exceed 14 cm unless a reduction in scale is possible.

Echocardiograms: Since these will be reproduced at a width of 7 cm or less all unnecessary or irrelevant detail (such as electronic writing) should be removed. Labelling must be superimposed directly on to the print itself and only where essential be shown on an accessory drawing. Echocardiograms obtained with 30° sector scans or bistable equipment or recorded on ultraviolet paper are not suitable for publication.

Figure legends must include an explanation of all abbreviations used in the Figure.

Copyright permission to reproduce material published elsewhere must be obtained in writing and acknowledged in the manuscript.

Proofs of articles accepted for publication will be sent for the author's approval. Proof corrections should be kept to a minimum.

Notice to subscribers

British Heart Journal is published monthly. The annual subscription rates are £97.00 inland and £113.00 overseas (USA $182·00). Combined rate: *British Heart Journal* and *Cardiovascular Research* £184 inland and £214 overseas (USA $350·00). Orders should be sent to The Subscription Manager, *British Heart Journal*, BMA House, Tavistock Square, London WC1H 9JR. Orders can also be placed with any leading subscription agent or bookseller. Subscribers may pay for their subscriptions by Access, Visa, or American Express by quoting on their order the credit or charge card preferred together with the appropriate personal account number and the expiry date of the card. (For the convenience of readers in the USA subscription orders ($182) with or without payment may also be sent to British Medical Journal, Box 560B, Kennebunkport, Maine 04046. All inquiries, however, must be addressed to the Publisher in London.) **All copies are despatched by air-speed.** First class rates available on request.

COPYRIGHT © 1989 by the *British Heart Journal*. All rights reserved. No part of this publication may be reproduced, stored in a retrieval system, or transmitted in any form or by any means, electronic, mechanical, photocopying, recording, or otherwise, without the prior permission of the *British Heart Journal*.

Second class postage paid, Rahway NJ Postmaster: send address changes to: British Heart Journal c/o Mercury Airfreight International Ltd Inc, 2323 Randolph Avenue, Avenel, NJ 07001, USA.

11.12.90

tober 1989 Vol 62 No 4

acm

25

British Heart Journal

monthly journal of cardiology
ublished in association with
he British Cardiac Society

Cuk-H0600-25-P25740

Protective effect of collateral vessels during coronary angioplasty *M S Norell, J P Lyons, J E Gardener, C A Layton, R Balcon* **241**

Impairment of diastolic function by shortened filling period in severe left ventricular disease *K S K Ng, D G Gibson* **246**

Influence of respiratory variations on right ventricular function *J L Caplin, W D Flatman, L Dyke, M N Wiseman, D S Dymond* **253**

Diagnosis of ventricular septal rupture after myocardial infarction: value of colour flow mapping *J Smyllie, K Dawkins, N Conway, G R Sutherland* **260**

Patterns of coronary artery disease in post-infarction ventricular septal rupture *J D Skehan, C Carey, M S Norrell, M de Belder, R Balcon, P G Mills* **268**

Cigarette smoking and non-fatal myocardial infarction in women: is the relation independent of coronary artery disease? *D S Freedman, H W Gruchow, J A Walker, S J Jacobsen, A J Anderson, K A Sobocinski, J J Barboriak* **273**

Superior QRS axis in ventricular septal defect *N J Shaw, M J Godman, A Hayes, G R Sutherland* **281**

Doppler flow characteristics in the assessment of pulmonary artery pressure in ductus arteriosus *A B Houston, M K Lim, W B Doig, J Gnanapragasam, E N Coleman, M P G Jamieson, J C S Pollock* **284**

Cross sectional echocardiographic anatomy of common atrioventricular valve in atrial isomerism *J Arisawa, S Morimoto, J Ikezoe, S Hamada, T Kozuka, T Sano, M Ogawa, H Matsuda, Y Kawashima* **291**

Quantitative effects of speckle reduction on cross sectional echocardiographic images *R J Massay, R B Logan-Sinclair, J C Bamber, D G Gibson* **298**

Magnetic resonance imaging at a high field strength of ventricular septal defects in infants *E J Baker, V Ayton, M A Smith, J M Parsons, E J Ladusans, R H Anderson, M N Maisey, M Tynan, N L K Fagg, P B Deverall* **305**

Dilatation with progressively larger balloons for severe stenosis of the pulmonary valve presenting in the late neonatal period and early infancy *S A Qureshi, E J Ladusans, R P Martin* **311**

The natural course of supravalvar aortic stenosis and peripheral pulmonary artery stenosis in Williams's syndrome *N G Giddins, J P Finley, M A Nanton, D L Roy* **315**

Family studies of congenital heart block associated with Ro antibody *W M H Behan, P O Behan, J M Reid, W Doig, J Gairns* **320**

British cardiology
  Crisis in cardiovascular research in Britain *M F Oliver* **325**

Notices **328**

Correction: Right ventricular infarction: diagnostic accuracy of electrocardiographic right chest leads V3R to V7R investigated prospectively in 43 consecutive fatal cases from a coronary care unit *H R Andersen, E Falk, D Nielsen* **328**

CALCUTTA UNIVERSITY CENTRAL LIBRARY

British Medical Association

ASTM CODEN: BHJUAV 62(4) 241–328 (1989)

British Heart Journal

P, 25, 740

EDITOR Dennis Krikler ASSISTANT EDITORS M J Davies, Kim Fox, Peter Mills

EDITORIAL COMMITTEE
Clive P Aber Kate Bull Keith Dawkins Alan B Houston Barry R Keeton Michael Marmot
Alexander L Muir Paul J Oldershaw Philip A Poole-Wilson David B Shaw
Tom Treasure David E Ward John Watkins Peter Wilde
Editor: *British Medical Journal* Editor: *Cardiovascular Research*

TECHNICAL EDITOR Jane Dawson EDITORIAL ASSISTANT Anne Oliver
STATISTICAL ADVISER Stephen J W Evans

Notice to contributors

Papers relating to the heart and circulation should be sent in triplicate to the Editor, British Heart Journal, BMA House, Tavistock Square, London WC1H 9JR, and be prepared according to the *Uniform requirements for manuscripts submitted to biomedical journals* (Vancouver agreement) (*Br Med J* 1988;**296**:401–5). Authors are asked to complete a copy of the checklist provided (1989;**61**:131–2 (January issue)) when submitting their manuscripts for publication. The reference number given on the acknowledgement postcard sent out by the editorial office should be quoted on all subsequent correspondence and telephone inquiries. A covering letter must be signed by all authors stating that they have seen and approved the paper and that the work has not been, and will not be, published elsewhere. All authors will be required to transfer copyright of their articles to the journal before publication. (All material for possible publication (including Letters to the Editor) *must* be typed in *double spacing* with 4 cm margins.)

Ethical standards
Authors are expected to comply with the code of ethics known as the Declaration of Helsinki. Where appropriate, manuscripts should include a statement that the research protocol has been approved by the locally appointed ethics committee and that the informed consent of the subjects has been obtained.

Case reports should convey only the essential facts of a case and the discussion and bibliography be kept to a minimum. They should have no more than three authors, should not exceed 1500 words, and include no more than two Figures.

Abbreviations should *not* be used in the text, except for mathematical calculations and units of measurement.

References must be cited precisely according to the Vancouver agreement and be typed in *double spacing*. As a general rule, no more than three references should be cited for any one statement.

Authors are responsible for the accuracy of any references cited: these should be checked at source or with the listing in Index Medicus.

Units of measurement
All haematological and clinical chemistry measurements should be given as SI units. Blood pressures should be given in mm Hg. Measurements of length, height, weight, and volume should be reported in metric units and temperatures should be reported in degrees Celsius.

Tables must be typed on separate sheets and not in the text. Titles should be provided, and all abbreviations used must be given in full in a footnote.

Illustrations (for general requirements, please refer to *Br Heart J* 1984; **51:** 1–6).

Electrocardiograms: Black and white prints only should be sent and not the original tracings. If several tracings are grouped in a single Figure only a few complexes should be shown; the width should not exceed 14 cm unless a reduction in scale is possible.

Echocardiograms: Since these will be reproduced at a width of 7 cm or less all unnecessary or irrelevant detail (such as electronic writing) should be removed. Labelling must be superimposed directly on to the print itself and only where essential be shown on an accessory drawing. Echocardiograms obtained with 30° sector scans or bistable equipment or recorded on ultraviolet paper are not suitable for publication.

Figure legends must include an explanation of all abbreviations used in the Figure.

Copyright permission to reproduce material published elsewhere must be obtained in writing and acknowledged in the manuscript.

Proofs of articles accepted for publication will be sent for the author's approval. Proof corrections should be kept to a minimum.

Notice to subscribers

British Heart Journal is published monthly. The annual subscription rates are £97.00 inland and £113.00 overseas (USA $182·00). Combined rate: *British Heart Journal* and *Cardiovascular Research* £184 inland and £214 overseas (USA $350·00). Orders should be sent to The Subscription Manager, *British Heart Journal*, BMA House, Tavistock Square, London WC1H 9JR. Orders can also be placed with any leading subscription agent or bookseller. Subscribers may pay for their subscriptions by Access, Visa, or American Express by quoting on their order the credit or charge card preferred together with the appropriate personal account number and the expiry date of the card. (For the convenience of readers in the USA subscription orders ($182) with or without payment may also be sent to British Medical Journal, Box 560B, Kennebunkport, Maine 04046. All inquiries, however, must be addressed to the Publisher in London.) **All copies are despatched by air-speed.** First class rates available on request.

COPYRIGHT © 1989 by the *British Heart Journal*. All rights reserved. No part of this publication may be reproduced, stored in a retrieval system, or transmitted in any form or by any means, electronic, mechanical, photocopying, recording, or otherwise, without the prior permission of the *British Heart Journal*.

Second class postage paid, Rahway NJ Postmaster: send address changes to: British Heart Journal c/o Mercury Airfreight International Ltd Inc, 2323 Randolph Avenue, Avenel, NJ 07001, USA.

Br Heart J 1989;**62**:241–5

Protective effect of collateral vessels during coronary angioplasty

MICHAEL S NORELL, JOHN P LYON, [illegible]HN E GARDENER, CLIVE A LAYTON,
RAPHAEL BALCON

From the Cardiac Department, London Chest Hospital, London

SUMMARY To assess the potential protective role of collateral vessels 27 patients undergoing angioplasty of the left anterior descending coronary artery were studied by intravenous digital subtraction left ventriculography. Fifteen patients had no collateral vessels (group 1) and 12 had some degree of collateral supply (group 2). During balloon inflation ST segment elevation in group 1 (4·9 mm) was significantly greater than that in group 2 (0·9 mm). Similarly the reduction in left ventricular ejection fraction was significantly greater in group 1 (24%) than in group 2 (12%). Both the size of ST segment elevation and the fall in ejection fraction correlated inversely with the extent of the collateral supply ($r = -0{\cdot}680$ and $r = -0{\cdot}446$ respectively). During balloon occlusion of the anterior descending coronary artery the percentage shortening of the anterior and apical segments fell in both groups but apical shortening fell to a lesser extent in group 2. An additional reduction in anterobasal contraction was confined to group 1.

Electrocardiographic and ventriculographic manifestations of ischaemia produced by balloon inflation during angioplasty are less pronounced when collateral vessels are present. This suggests that the collateral circulation can protect myocardium at risk of ischaemia after coronary occlusion.

The extent to which collateral vessels can protect the myocardium during coronary occlusion is not known. Many earlier studies were retrospective and attempted to relate the degree of left ventricular damage after thrombotic coronary occlusion to the subsequent arteriographic assessment of collateral circulation.[1 2] Coronary angioplasty, by producing transient, controlled coronary occlusion has allowed a prospective examination of both the angiographic development and the functional role of the collateral circulation.[3-5] We showed that global and regional left ventricular performance can be assessed during coronary angioplasty with intravenous digital subtraction ventriculography.[6] We used this technique to examine the degree to which collateral vessels protect the myocardium during transient coronary occlusion produced by balloon inflation.

Patients and methods

We studied 27 patients (22 men and five women, mean age 52). They belonged to a group described in a feasibility study that examined the effect of coronary angioplasty on left ventricular function.[6] They all had limiting angina despite optimum medical treatment. At the time of the study 23 patients were taking a β adrenergic blocking agent, 25 were taking a calcium antagonist, and 21 were taking nitrates. Seventeen patients were in class 3 of the Canadian Cardiovascular Society while the remaining 10 patients were in class 4.

All patients had single vessel coronary disease defined as at least a 70% reduction in luminal diameter affecting only the left anterior descending artery proximal to its first diagonal branch. The estimated severity of the lesions treated by angioplasty ranged from 70% to 99% (mean 89%). In all cases the stenoses allowed anterograde flow of contrast. Left ventriculography showed normal contraction in all patients, the mean ejection fraction being 75%.

COLLATERAL ASSESSMENT

Coronary arteriograms performed before the angioplasty procedure were reviewed by two observers to assess any collateral circulation. As is routine in our laboratory, selective arteriograms were performed in

Requests for reprints to Dr Michael S Norell, Cardiac Department, Harefield Hospital, Harefield, Middlesex UB9 6JH.

Accepted for publication 11 April 1989

multiple projections and we used 3–5 ml of contrast injected by hand over 1–3 seconds. Cinerecording was continued after each injection until it was apparent that there was no further vessel opacification. Any collateral circulation was then measured by a method[4] that grades collaterals according to the extent to which the epicardial arterial segment distal to the target stenosis is retrogradely opacified: no collateral vessels visible, 0; collateral vessels visible, 1; <50% opacification of distal segment, 2; >50% opacification of distal segment, 3.

ANGIOPLASTY PROCEDURE

Patients received premedication with an oral nitrate, calcium antagonist, and dipyridamole an hour before the angioplasty procedure. Angioplasty was performed via the femoral approach with 2·5 mm or 3 mm balloon catheters and steerable guide wires. Patients underwent 3–7 balloon inflations each for 20 to 60 seconds at inflation pressures ranging from 5–10 atm (1 atm ≈ 101 kPa). The electrocardiogram was allowed to return to baseline before subsequent inflations.

ELECTROCARDIOGRAPHY

A 12 lead electrocardiogram at a paper speed of 25 mm/s was monitored throughout the angioplasty procedure. The time of balloon inflation and deflation was marked, as was the onset of digital ventriculography. Any change in ST segment (> 1 mm) was measured with a graticule 80 ms after the J point and the maximum change in any lead recorded.

DIGITAL VENTRICULOGRAPHY

Digital subtraction left ventriculography after contrast injection into the right atrium was performed before and during (>20 s) either the third (21 patients) or fourth (six patients) balloon inflation, according to a previously described method.[6] We injected 40 ml of non-ionic contrast medium (iohexol; Omnipaque 350 mg iodine/ml, Nycomed) at 17 ml/s through a 5 French pigtail catheter (Superflow, Cordis) during held inspiration. Ventriculograms were acquired at 12·5 frames/s on to a 256 × 256 pixel matrix with a Siemens Digitron connected on line to a Siemens Elema Angioskop D imaging system. End diastolic and subsequent end systolic frames were selected, excluding extrasystoles, and their outline was manually digitised by an observer blinded to the patient's collateral circulation. An area-length method was used to calculate left ventricular volumes[7] and hence ejection fraction. To assess regional left ventricular wall motion we used a method that calculates the percentage systolic shortening of radii from the end systolic centre of gravity to the end diastolic perimeter.[8] This was modified so that the results could be expressed as percentage shortening for each of five left ventricular regions: anterobasal, anterior, apical, inferior, inferobasal.[6]

STATISTICAL ANALYSIS

Patients were divided into two groups depending on whether or not any collateral supply could be seen angiographically. Statistical tests included paired or unpaired Student's *t* test as appropriate. To relate electrocardiographic or ventriculographic changes to the collateral grade, Spearman's rank correlation was used.

This study was approved by the ethics committee of the National Heart and Chest Hospitals and all patients gave written informed consent.

Results

ASSESSMENT OF COLLATERALS

Fifteen of the 27 patients studied had no angiographically demonstrable collateral vessels (group 1, collateral grade = 0) while the remaining 12 patients had some degree of collateral supply (group 2, mean collateral grade = 1·7). The severity of coronary obstruction was greater in group 2 than in group 1 (94% *v* 86%, $p < 0{\cdot}05$).

ELECTROCARDIOGRAPHY

During balloon inflation in the left anterior descending coronary artery the degree of ST elevation in group 1 (mean = 4·9 mm, range 0–9 mm) was greater than that in group 2 (mean = 0·9 mm, range 0–5 mm, $p < 0{\cdot}001$). There was an inverse correlation between the magnitude of ST segment elevation and the collateral grade ($r = -0{\cdot}680$, $p < 0{\cdot}001$, fig 1).

GLOBAL LEFT VENTRICULAR PERFORMANCE

Before angioplasty the left ventricular ejection fraction was similar in the two groups (group 1 74%, group 2 78%, NS). During balloon inflation ejection fraction decreased to 50% in group 1 ($p < 0{\cdot}001$) but only to 66% in group 2 ($p < 0{\cdot}001$). This fall was significantly larger in group 1 than in group 2 (24% *v* 12%, $p < 0{\cdot}01$).

There was an inverse correlation between the fall in left ventricular ejection fraction during balloon inflation and the extent of the collateral supply ($r = -0{\cdot}446$, $p < 0{\cdot}01$, fig 2).

REGIONAL LEFT VENTRICULAR PERFORMANCE (TABLE 1)

Before angioplasty there were no significant differences between the two groups in left ventricular regional shortening. During balloon inflation in the anterior descending artery anterior and apical

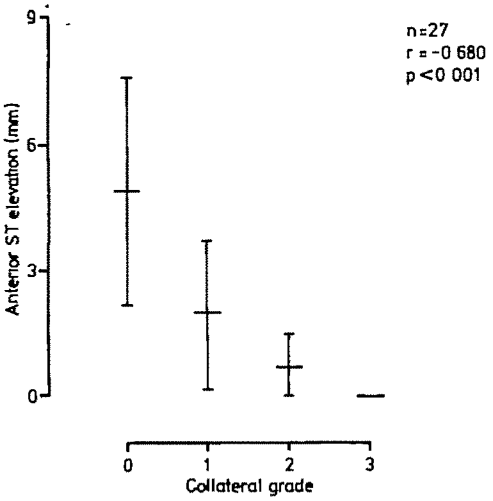


Fig 1 *Relation between the extent of collateral supply (collateral grade) and anterior ST segment elevation (mean (SD)) during balloon inflation in the left anterior descending artery.*

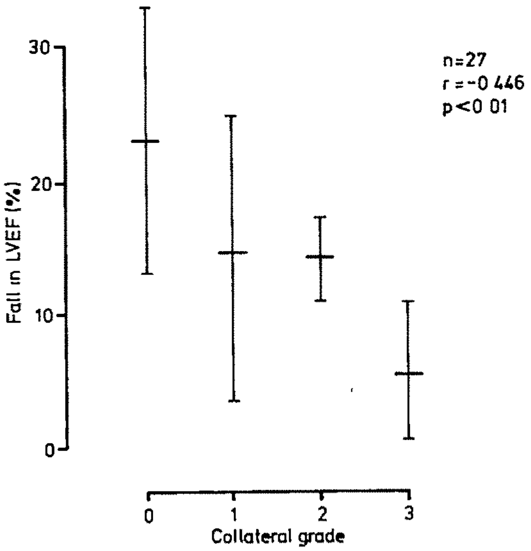


Fig 2 *Relation between the extent of collateral supply (collateral grade) and the reduction in left ventricular ejection fraction (mean (SD)) (LVEF) during balloon inflation in the left anterior descending artery.*

regional shortening decreased in both groups (group 1 38% to 12%, $p < 0{\cdot}001$; 51% to 11%, $p < 0{\cdot}001$ respectively and group 2 42% to 19%, $p < 0{\cdot}001$; 55% to 26%, $p < 0{\cdot}001$ respectively). Anterobasal shortening decreased significantly only in group 1 (37% to 24%, $p < 0{\cdot}01$) and not in group 2 (38% to 33%, NS). Apical shortening during balloon inflation was also better preserved in group 2 (26%) than in group 1 (11%, $p < 0{\cdot}05$).

Shortening in the inferior region during angioplasty did not change significantly in either group (group 1 48% to 43%, NS; group 2 48% to 53%, NS), but inferobasal contraction was equally enhanced in both groups (group 1 8% to 23%, $p < 0{\cdot}01$; group 2 5% to 27%, $p < 0{\cdot}01$).

The reduction in anterobasal, anterior, and apical regional shortening during balloon occlusion of the anterior descending coronary artery tended to be larger in those patients without collateral vessels (group 1) than in group 2, but these differences were not significant (table 2).

Table 2 *Reduction in left ventricular segmental shortening (%, mean (SD)) during angioplasty of the anterior descending coronary artery in patients without (group 1) or with (group 2) collateral vessels*

Left ventricular segment	*Group 1 (n = 15)*	*Group 2 (n = 12)*	*p*
Anterobasal	13 (15)	5 (12)	NS
Anterior	26 (13)	23 (17)	NS
Apical	40 (18)	29 (20)	NS
Inferior	5 (18)	+5 (10)	NS
Inferobasal	+15 (18)	+22 (23)	NS

Positive (+) value indicates an increase in segmental shortening

Discussion

Previous studies of the potential protective role of collateral vessels have related the degree of left ventricular dysfunction after thrombotic coronary

Table 1 *Comparison of left ventricular regional shortening (%, mean (SD)) before and during angioplasty of the anterior descending coronary artery in patients without (group 1, n = 15) or with (group 2, n = 12) collateral vessels*

	Before PTCA			*During PTCA*		
LV segment	*Group 1*	*Group 2*	*p*	*Group 1*	*Group 2*	*p*
Anterobasal	37 (9)	38 (11)	NS	24 (13)	33 (17)	NS
Anterior	38 (9)	42 (11)	NS	12 (11)	19 (24)	NS
Apical	51 (8)	55 (12)	NS	11 (14)	26 (22)	<0 05
Inferior	48 (13)	48 (15)	NS	43 (14)	53 (13)	NS
Inferobasal	8 (11)	5 (14)	NS	23 (17)	27 (23)	NS

LV, left ventricular; PTCA, percutaneous transluminal coronary angioplasty.

occlusion to the extent of the collateral circulation that was later apparent. Although some found that left ventricular damage was reduced when there was an extensive collateral system[1 2] others did not.[9] Such retrospective studies have to be viewed with caution because the state of the collateral circulation at the time of coronary occlusion is unknown. Coronary angioplasty, however, allows further assessment of the development and functional role of these vessels. Collateral vessels that were not apparent before angioplasty were seen during balloon inflation,[3 4] and those present before the procedure disappeared after successful angioplasty.[10] When the haemodynamic contribution of collaterals to the coronary circulation was examined during angioplasty,[11] the pressure distal to an inflated angioplasty balloon was shown to relate to the extent of the collateral supply shown by angiography.

We assessed the function of the collateral circulation and showed that the manifestations of myocardial ischaemia during balloon occlusion of the anterior descending artery were reduced when collateral vessels filled the distal arterial segment. Furthermore, we showed that the degree of ischaemia produced during balloon inflation correlated with the extent of the collateral supply. These findings accord with those of others.[5] Cohen and Rentrop examined the occurrence of anginal pain, together with the degree of ST segment elevation and echocardiographic evidence of left ventricular dysfunction during balloon inflation. They related these findings to the collateral supply apparent angiographically during balloon occlusion and also showed that these indices of myocardial ischaemia were reduced in the presence of collateral vessels.

The present study differs from that of Cohen and Rentrop. Although we used a similar system to grade the collateral supply,[4] we assessed the collateral circulation before, rather than during, balloon inflation. Because the ability to demonstrate collateral vessels angiographically is dependent on the degree of proximal arterial obstruction,[2 9] we may have underestimated the collateral state before balloon occlusion. However, other workers have shown that although the collateral filling of a distal arterial segment may increase abruptly after balloon occlusion, the protective effect of such apparently increased flow is variable.[3]

We found that even when there was an extensive collateral supply ventriculographic abnormalities still occurred during balloon inflation. This also accords with the finding of others who noted the development of angina, ST segment elevation, and left ventricular dysfunction during balloon occlusion despite the complete opacification of the index artery by collateral vessels.[5] This suggests that even an abundant collateral supply may be inadequate to protect completely a potentially ischaemic myocardium. Previous studies also showed that collateral vessels do not necessarily reduce the extent of exercise induced myocardial ischaemia[2 12 13] or the subsequent incidence of cardiac events.[14] Furthermore, because all the patients in the present study were limited by angina before angioplasty, the finding that their collateral circulation was not sufficient is not unexpected.

The extent of a collateral circulation is usually assessed with selective coronary arteriography. This method itself may have limitations because several factors can influence the appearance of collateral vessels after selective injection of contrast into a coronary artery. Because the opacification of collateral vessels depends on a pressure gradient across the coronary beds, the pressure used for contrast injection and the degree of proximal obstruction are especially relevant in determining the appearance of collaterals. The presence of vasodilator drugs and the resolution of the angiographic equipment are also important.

We made no attempt to standardise the pressure and flow rate of selective coronary injections in our patients; we used our routine technique for diagnostic coronary angiography. All our patients were given vasodilators (a nitrate and a calcium antagonist) before angioplasty to ameliorate any ischaemia and reduce any tendency to coronary spasm during the procedure. The specific effect of such drugs on collateral vessels is unclear.[15 16] Thus although an angiographic assessment of collateral vessels may have limitations, it does indicate the extent of the collateral circulation and this is borne out by the results of our study.

Coronary angioplasty, by producing reversible, controlled coronary occlusion, allowed a prospective study of the function of collateral vessels. The electrocardiographic and ventriculographic manifestations of ischaemia during balloon inflation were less pronounced in patients in whom a collateral circulation was seen. This supports the view that such vessels can protect myocardium at risk of ischaemia after coronary occlusion.

MSN was supported by the British Heart Foundation.

References

1 Fulton WFM. Anastomotic enlargement and ischaemic myocardial damage. *Br Heart J* 1964;**26**:1–15.

2 Freedman SB, Dunn RF, Bernstein L, Morris J, Kelly DT. Influence of coronary collateral blood flow on the development of exertional ischaemia and Q wave

infarction in patients with severe single vessel disease. *Circulation* 1985;71:681–6.

3 Hill JA, Feldman RL, MacDonald RG, Pepine CJ. Coronary artery collateral visualisation during acute coronary occlusion. *Am J Cardiol* 1985;55:1216–8.

4 Rentrop KP, Cohen M, Blanke H, Phillips RA. Changes in collateral channel filling immediately after controlled coronary artery occlusion by an angioplasty balloon in human subjects. *J Am Coll Cardiol* 1985;5:587–92.

5 Cohen M, Rentrop KP. Limitation of myocardial ischaemia by collateral circulation during sudden controlled coronary artery occlusion in human subjects: a prospective study *Circulation* 1986;74·469–76.

6 Norell MS, Lyons JP, Gershlick AH, *et al.* Assessment of left ventricular performance during percutaneous transluminal coronary angioplasty: a study by intravenous digital subtraction ventriculography. *Br Heart J* 1988;59:419–28.

7 Sandler H, Dodge HT. The use of single plane angiocardiograms for the calculation of left ventricular volume in man. *Am Heart J* 1968;75:325–34.

8 Rickards A, Seabra-Gomes R, Thurston P. The assessment of regional abnormalities of the left ventricle by angiography. *Eur J Cardiol* 1977;5:167–82.

9 Elayda MA, Mathur VS, Hall RJ, *et al.* Collateral circulation in coronary artery disease. *Am J Cardiol* 1985;55:58–60.

10 Legrand V, Aueron FM, Bates ER, *et al.* Reversibility of coronary collaterals and alteration in regional coronary flow reserve after successful angioplasty. *Am J Cardiol* 1984;54:453–4.

11 Probst P, Zangl W, Pachinger O. Relation of coronary arterial occlusion pressure during PTCA to presence of collaterals. *Am J Cardiol* 1985;55:1264–9.

12 Tubau JF, Chaitman BR, Bourassa WG, Lesperance J, Dupras G. Importance of coronary collateral circulation in interpreting exercise test results *Am J Cardiol* 1981;47:27–32.

13 Kolibash AJ, Bush CA, Wepsic RA, *et al.* Coronary collateral vessels: spectrum of physiologic capabilities with respect to providing rest and stress myocardial perfusion, maintenance of left ventricular function and protection against infarction. *Am J Cardiol* 1982; 50:230–8.

14 Nestico PF, Hakki AH, Meissner MD, *et al.* Effect of collateral vessels on prognosis in patients with one vessel coronary artery disease. *J Am Coll Cardiol* 1985;6.1257–63.

15 Bass TA, O'Brien JT, Conetta DA, Perryman RA, Miller AB. Dynamic appearance of collaterals during transluminal coronary angioplasty [Abstract]. *Circulation* 1984;70(suppl II):36.

16 Weintraub WS, Hattori S, Akizuki S, *et al.* Influence of nifedipine on collateral blood flow during acute ischaemia in the dog. *J Am Coll Cardiol* 1984;3:334–40.

Br Heart J 1989;62:246–52

Impairment of diastolic function by shortened filling period in severe left ventricular disease

KELVIN S K NG, DEREK G GIBSON

From the Cardiac Department, Brompton Hospital, London

SUMMARY A dilated left ventricle with reduced ejection fraction is usually attributed to impaired systolic function. To investigate the possibility that ventricular filling might also be disturbed, M mode echocardiograms, phonocardiograms, and Doppler cardiograms were recorded in 30 patients with ventricular disease of varying cause. All but four had functional mitral regurgitation. The size of the left ventricular cavity was increased in all and peak velocity of circumferential fibre shortening was reduced. Diastolic abnormalities included a short isovolumic relaxation time, and, on digitised M mode, a reduced rate of dimension increase and of posterior wall thinning. Although the timing of aortic valve closure was normal, mitral regurgitation persisted beyond it by 95 (35) ms and beyond mitral valve opening by 60 (40) ms. This reduced the effective filling time (the interval when the mitral valve was open and mitral regurgitation was absent) to <200 ms in seven patients. The effective filling time correlated closely with the RR interval, the regression equation indicating a reduction of 80 ms for each 100 ms fall in RR interval. It was also independently shortened by 2 ms a year with increasing age. The effective left ventricular filling time may thus be very short in patients with left ventricular cavity dilatation and functional mitral regurgitation.

It is suggested that when diastolic function is also abnormal, this short filling time may physically limit ventricular inflow. Its close relation to heart rate might contribute to the therapeutic effect of β blockade in such patients.

A dilated left ventricular cavity with reduced ejection fraction is common in the late stages of heart disease, and is usually held to be caused by depressed systolic function.[1] Such patients are often said to be in "heart failure" and are treated with digitalis, diuretics, and vasodilators. A minority, however, respond favourably to β adrenoceptor blocking drugs[2] and this would be surprising if systolic disease were the only reason why function was impaired. It is possible, therefore, that other pathogenic mechanisms are involved, and we have attempted to identify them by investigating how filling, rather than ejection, can be disturbed in these patients.

Patients and methods

The records of 30 unselected patients (aged from 12 to 75, 22 men) with dilatation of the left ventricular cavity and reduced shortening fraction were examined retrospectively. The underlying diagnosis was coronary artery disease in 11, dilated cardiomyopathy in three, presumed myocarditis in two, and there were single cases associated with polyarteritis nodosa, Churg-Strauss syndrome, sarcoidosis, irradiation, and alcoholic cirrhosis. Coronary artery disease was diagnosed by coronary arteriography or directly at necropsy or at the time of cardiac transplantation. In the remaining nine patients, three of whom had long standing hypertension, we cannot say whether or not coronary artery disease was present, because there was no clinical indication for coronary arteriography. All the patients were in sinus rhythm and five had left bundle branch block. All were taking diuretics, either frusemide or bumetanide, along with amiloride in nine or metolazone in one. Twenty were taking captopril, three a theophylline preparation, two isosorbide, and one nifedipine, while five were treated with a digitalis preparation.

Cross sectional echocardiography in multiple cuts

Requests for reprints to Dr Derek G Gibson, Brompton Hospital, Fulham Road, London SW3 6HP.

Accepted for publication 18 April 1989

showed uniform enlargement of the left ventricular cavity and a reduced ejection fraction in all, and excluded a ventricular aneurysm or other major abnormality of regional wall motion. M mode echocardiograms were recorded with simultaneous phonocardiograms and electrocardiograms at a paper speed of 100 mm/s at the level of the tips of the mitral leaflets. Clear, continuous echoes were obtained from the endocardial surfaces of the left side of the septum and the endocardium of the posterior wall. Separate echograms were recorded of the mitral valve at the level at which cusp separation at the start of filling and closure at the onset of systole could most clearly be seen (fig 1a) and of the aortic echogram, from which the aortic component of the second heart sound (A_2) was identified as the onset of the first high frequency vibration of the component coinciding with cusp apposition. Continuous wave Doppler recordings were made with Doptek equipment, again with simultaneous phonocardiograms and electrocardiograms, at a paper speed of 100 mm/s to show the timing of functional mitral regurgitation (present in all but four patients), and separately, of early diastolic forward flow across the mitral valve.

From the M mode echocardiograms we measured the dimensions of the left ventricular cavity synchronously with the Q wave of the electrocardiogram (end diastolic) and with A_2 (end ejection), from the leading edges. We digitised the records[3] to give plots of the left ventricular dimension and posterior wall thickness along with their rates of change. The timing of A_2 was superimposed on all digitised records, and the interval A_2 to peak rate of dimension increase was measured. We took the isovolumic relaxation time to be the interval between the onset of the first high frequency component of A_2 on the phonocardiogram and the initial cusp separation on the mitral echogram.[4] We estimated the interval over which the mitral valve was open (mitral valve open time)[5] as that from the initial cusp separation at the onset of diastole to the final apposition at the start of the succeeding systole. The left ventricular ejection time was determined from the aortic echograms and the QA_2 interval from the electrocardiogram and phonocardiogram. Values of QA_2 from patients with left bundle branch block were not included in the analysis.

On the Doppler recording, we measured the overall duration of the mitral regurgitant signal (fig 1b) and also the two intervals from Q to the onset of the regurgitant signal and from A_2 to its end. On the trace of forward mitral flow we measured the interval from A_2 to the time of peak flow velocity.

Preliminary examination of the records showed that the times of onset and end of mitral regurgitation bore no fixed relation to those of mitral opening or closure, the regurgitation signal sometimes starting before mitral closure at the start of systole and often persisting beyond mitral opening at its end (fig 1). The interval from mitral opening to the end of regurgitation (interval A) was thus measured as the difference between the intervals A_2 to the end of

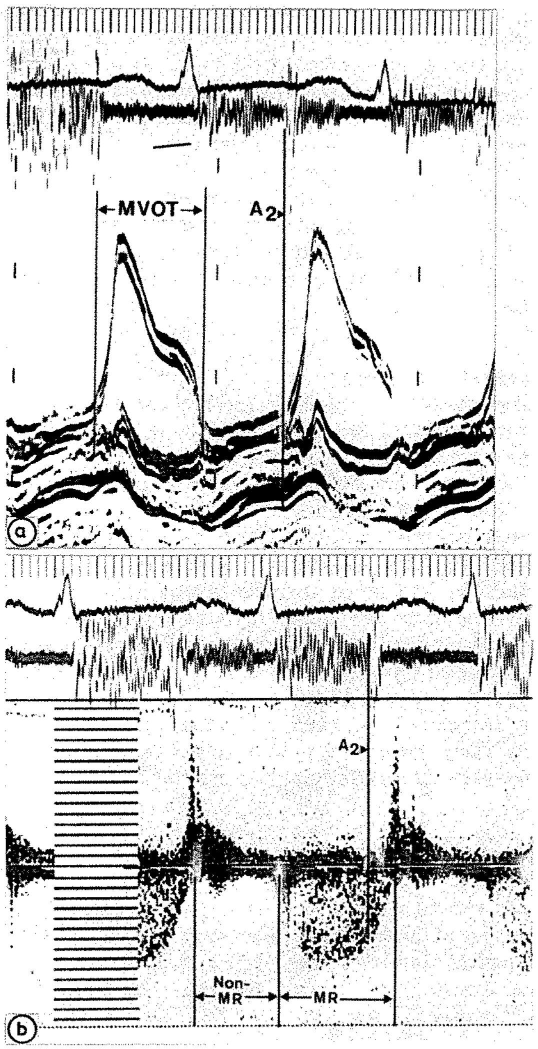


Fig 1 *(a) Mitral echogram from a patient with cardiomyopathy. Mitral valve open time is indicated (MVOT). Note that mitral cusp separation at the start of diastole is synchronous with aortic valve closure (A_2). (b) Continuous wave Doppler recording from the same patient, showing mitral regurgitation (MR). Its duration and that of the interval between pulses of regurgitation (non-MR) are indicated. Note that regurgitation continues for approximately 70 ms beyond A_2. (Full scale deflection 16 kHz).*

regurgitation and A_2 to mitral opening. The relation between the onset of regurgitation and mitral closure at the start of systole (interval B) was measured as the difference between the two intervals—Q to mitral closure and Q to onset of regurgitation. We defined effective filling time as the interval during which (*a*) the mitral valve was open and (*b*) mitral regurgitation had ceased, and derived it as mitral valve opening time less the sum of intervals A and B. In patients without functional mitral regurgitation, effective filling time was taken to be equal to mitral valve open time.

STATISTICAL ANALYSIS

All values were based on the mean of three determinations, except those of QA_2, which, in line with the recommendations of Lewis *et al*[6] were based on 10. Where appropriate, values were compared with normal values and their 95% confidence intervals previously reported by us. Differences between mean values were examined by calculating 95% confidence intervals,[7] and linear correlation was performed by the method of least squares. Estimates of reproducibility were based on independent determinations of all measurements by each co-author. Reproducibility was expressed as the mean (SD) of the differences between individual determinations and their mean.[8] We have recorded values for measurements underlying our conclusions.

Results

LEFT VENTRICULAR SYSTOLIC FUNCTION

The size of the left ventricular cavity was increased in all patients (mean (1 SD) 7·1 (0·3) cm) at end diastole and 6·3 (0·7) cm at end ejection. The mean left ventricular ejection time was 235 (30) ms, and the values correlated with the RR interval (table). The mean value of the QA_2 intervals was 375 (50) ms, with a reproducibility of 0 (8) ms, and again this correlated with the RR interval (table) but not with age. The corresponding regression relation with heart rate was:

$$QA_2 = 510 - 1{\cdot}65\ (\text{heart rate})\ \text{ms},$$

the standard errors of the estimate was 30 ms, and those of the slope and intercept were 0·36 and 35 respectively. The slope and intercept of this equation did not differ significantly from normal values previously reported by Lewis *et al.*[6] The mean value of peak velocity of circumferential fibre shortening (VCF) was 0·6 (0·2)/s. In all the patients, it was below the normal range of 1·2–2·0/s.

MITRAL VALVE MOTION

The isovolumic relaxation time was 25 (35) ms (reproducibility 1 (7) ms), significantly less than the normal value of 60 (10) ms; only 11 patients were within the normal range, values being abnormally short in the remainder. The mean mitral valve open time was 345 (130) ms (reproducibility −3 (10)) and values correlated strongly with heart rate (table). Mitral closure followed the Q wave by 75 (55) ms, an interval unrelated to heart rate.

DOPPLER MEASUREMENTS

Mitral regurgitation was detected by continuous wave Doppler in 26 of the 30 patients. It lasted 400 (70) ms, reproducibility −3 (10), with values above 500 ms in three patients. It correlated weakly with RR interval and rather more strongly with age (table). The interval between the pulses of regurgitation (non-MR interval) was 290 (120) ms (reproducibility 3 (10) ms) which correlated strongly with RR interval (table). The mean interval between the Q wave and the onset of mitral regurgitation was 65 (20) ms, and between A_2 and its end it was 95 (35) ms, (reproducibility 0 (7) ms). Neither was related to heart rate, though the time from A_2 to the end of mitral regurgitation increased with age (table).

EFFECTIVE FILLING PERIOD

In all but three patients mitral regurgitation persisted for up to 160 ms after mitral valve opening (mean

Table *Determinants of ventricular function*

					Standard error		
Dependent variable (x)	*Independent variable (y)*	*r*	*Slope*	*Intercept*	*Slope*	*Intercept*	*Estimate*
Duration of MR	Age	0·53	2·0	290	0·68	38	54
A_2 to end of MR	Age	0·68	1·3	18	0·30	17	24
Non-MR interval	Mitral valve open time	0·87	1·0	69	0·11	36	68
Mitral valve open time	RR interval	0·78	0·82	−220	0·12	88	90
Non-MR interval	RR interval	0·87	0·75	−230	0·09	65	63
Effective filling time	RR interval	0·80	0·78	−260	0·12	83	84
QA_2 interval	RR interval	0·67	0·23	205	0·05	34	37
Ejection time	RR interval	0·50	0·11	160	0·04	26	28
Duration of MR	RR interval	0·43	0·21	250	0·09	66	66

MR, mitral regurgitation

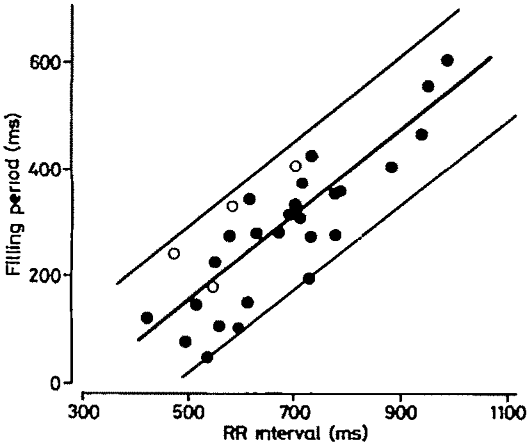


Fig 2 *Relation between RR interval and effective filling period. Limits are set at two standard errors of the estimate. Closed symbols represent results from patients with mitral regurgitation and open symbols from those without.*

60 (40) ms). By contrast, the onset of mitral regurgitation could precede or follow mitral closure, the mean interval between the two being 8 (40) ms. The mean value of effective filling period was thus 275 (135) ms, reproducibility 6 (17) ms, which again correlated strongly with the RR interval (table and fig 2). In seven patients the effective filling period was <200 ms. Their average age (45 (15)) was no different from that of the whole group. They all had functional mitral regurgitation. Two of them had myocarditis, one each had heart disease caused by coronary artery disease, irradiation, or polyarteritis nodosa, while a definite diagnosis had not been established in two. Two had left bundle branch block. In six, the RR interval was in the range 480–590 ms; in the seventh, it was 740 ms, and in this patient the effective filling period was short because mitral regurgitation lasted 560 ms, extending 160 ms beyond A_2.

DIGITISED M MODE ECHOCARDIOGRAMS

On the digitised M mode echocardiograms, the peak rate of dimension increase was 7·5 (3·8) cm/s. Seven values were within the normal range and the remainder were below. The rapid filling period was 150 (45) ms, with values below the normal range in 11 and above it in one. The peak rate of wall thinning was very low (3·5 (2) cm/s) and values from all but four patients were below the lower limit of normal. The interval from minimum cavity dimension to mitral opening was 3 (40) ms, which was not significantly different from normal. There was wide variation between patients, however: mitral opening was abnormally delayed in seven, and was premature, occurring up to 80 ms before minimum dimension, in six. Finally, phase relations between the peak rate of dimension increase and peak flow were abnormal during rapid filling, when the normal delay in peak filling velocity with respect to peak rate of dimension increase (50 (15) ms) was lost in 10 patients.

WITHIN PATIENT COMPARISONS

We recorded at two different heart rates in eight patients. With a mean fall in RR interval of 155 (110) ms, the non-MR interval shortened by 105 (130) (95% confidence interval 45 ms) and mitral valve open time by 105 (90) (95% confidence interval 60 ms), while isovolumic relaxation time, and the duration of mitral regurgitation and its persistence beyond A_2 were all unchanged.

Discussion

Although impaired systolic function is usually held to be the main cause of the dilated left ventricular cavity and reduced ejection fraction seen in patients with severe heart disease,[1] diastolic abnormalities have also been described. The peak rate of pressure decline during isovolumic relaxation was reduced[9] and the time constant of pressure fall was prolonged.[10] Although the peak rate of increase of ventricular volume during early diastole was usually normal,[11] the peak rate of dimension increase was often low, and in many patients the early rapid filling period was short.[9 12] Finally, left ventricular passive stiffness was increased, both when expressed as cavity compliance or as a myocardial stress-strain relation.[13] These abnormal measurements, however, do not necessarily define independent disturbances of diastole. When left ventricular filling pressure is raised, as it often has been in reported cases, isovolumic relaxation time may be very short or even zero,[4] so that the fundamental assumption underlying the use of the time constant of pressure fall as a measure of relaxation, namely that the ventricle is isovolumic for the period over which the calculation is made, does not necessarily apply. At a constant transmitral flow rate, the peak rate of dimension increase is inversely proportional to the square of the dimension, so on simple geometrical grounds it will be low when the ventricle is enlarged. "Normalisation" to unit dimension by calculating the velocity of circumferential fibre shortening or lengthening merely increases the discrepancy, making the peak rates of dimension increase sensitive to the cube of the dimension. Finally passive stiffness can only be calculated when pressure and volume increase together. This does not occur until late diastole when heart rate is low[14] and may not do so at all when it is rapid.

In our study, therefore, we examined the effective left ventricular filling period, an aspect of diastolic function that is independent of increased cavity size, heart rate, or isovolumic relaxation time. We defined it as the period during which the mitral valve was open and retrograde flow had ceased, assuming that there is no forward flow from atrium to ventricle in the presence of mitral regurgitation. In several patients, this effective filling period was very short, and in seven, it was <200 ms. In healthy individuals, left ventricular filling time varies with heart rate. It shortens with tachycardia caused by exercise or atrial pacing, reaching a minimum of 100 ms.[5] Ventricular filling may be very rapid, therefore, when diastolic function is normal. In patients with left ventricular hypertrophy and associated diastolic disease, filling time does not drop below 200 ms, even when heart rate is high; the extra filling time is found within the RR interval by shortening isovolumic relaxation time. Diastolic abnormalities in our patients differed from those seen in patients with hypertrophy. The isovolumic relaxation time was usually very short or even zero at rest rather than being increased, and the early diastolic filling period was either normal or short, rather than prolonged. Nevertheless, phase relations between transmitral flow velocity and dimension changes were often abnormal. Rapid wall thinning, intimately related to rapid ventricular filling under normal conditions,[15] was much lower than would have been expected from cavity dilatation alone. Mitral valve opening was often delayed in relation to minimum cavity dimension, indicating incoordinate relaxation.[16] Finally, changes in cavity shape, which also form a prominent part of normal ventricular adaptation to rapid filling, are likely to have been absent in our patients.[17] Superimposed on such abnormal diastolic function, therefore, a filling period of <200 ms might be expected to limit ventricular inflow directly.

A striking feature of the functional mitral regurgitation in our patients was that it lasted ≥500 ms. Though the QA_2 interval was normal, retrograde flow was prolonged beyond the end of ejection into what would normally have been isovolumic relaxation. In our patients, however, isovolumic relaxation was usually short or even zero. This led to the paradoxical finding in most that the mitral valve was open in the face of continuing regurgitation (fig 1). In addition, the excessive duration of the regurgitation was little affected by heart rate. Filling time thus became very sensitive to tachycardia, shortening by 80 ms for each 100 ms fall in RR interval. As heart rate rises, therefore, the cardiac cycle becomes increasingly occupied by mitral regurgitation, and filling time becomes disproportionately shortened (fig 2). This effect of heart rate was seen whatever the cause of the ventricular disease, pointing to the dilated cavity itself as a possible cause. The effect of age on the duration of mitral regurgitation and its continuation beyond A_2 suggests that filling might be more frequently disturbed in older patients, but we found no evidence of this. Presumably the duration of mitral regurgitation reflects the period during which myocardial tension develops in the left ventricle, though we do not know why this is so strikingly prolonged. Perhaps the time course of deactivation[18] is modified by the abnormal pattern of development of systolic stress in a dilated ventricle or by the loss of β adrenoceptive receptors found in "failing" human hearts removed at the time of transplantation.[19] Certainly, our results accord with the disturbed calcium handling described in vitro in myocardium from patients with severe ventricular disease.[20]

In some of our patients, therefore, cardiac output seemed to have been limited not directly by systolic disease but by ventricular inflow. When filling time is short, mean flow rates across the mitral valve must be rapid to maintain stroke volume, and this means that acceleration and deceleration rates must be correspondingly high. Such rapid changes in blood velocity must, on a simple physical basis, be accompanied by considerable pressure drops along the direction of flow. This leads to conditions closely resembling those seen in rheumatic mitral stenosis, when ventricular filling also depends on a high pressure difference between left atrium and left ventricle. In both conditions cardiac output may be low and arterial pressure maintained only by raised peripheral resistance, effectively increasing ventricular afterload. This may explain the reduced ejection rates seen in mitral stenosis and the tendency for cavity size and filling pressures to fall after successful operation.[21] Sometimes these changes may be very striking, with a remarkable increase in ejection fraction and fall in end diastolic pressure.[22] If ventricular function was modified in the same way in our patients, the low observed ejection fractions might have been caused in part by this secondary increase in resistance to ejection and not exclusively by left ventricular disease. These similarities could be summarised by suggesting that our patients had "temporal" mitral stenosis to emphasise how much they resemble those of the well recognised "spatial" variety.

The filling period was not short in all our patients. The heart rate was low in some and regurgitation not unduly prolonged in others. It would not have been possible to predict these differences in haemodynamic state from simple measurements of heart rate or cavity size. Yet they are not purely of theoretical importance because they suggest approaches to treatment. If the filling period does

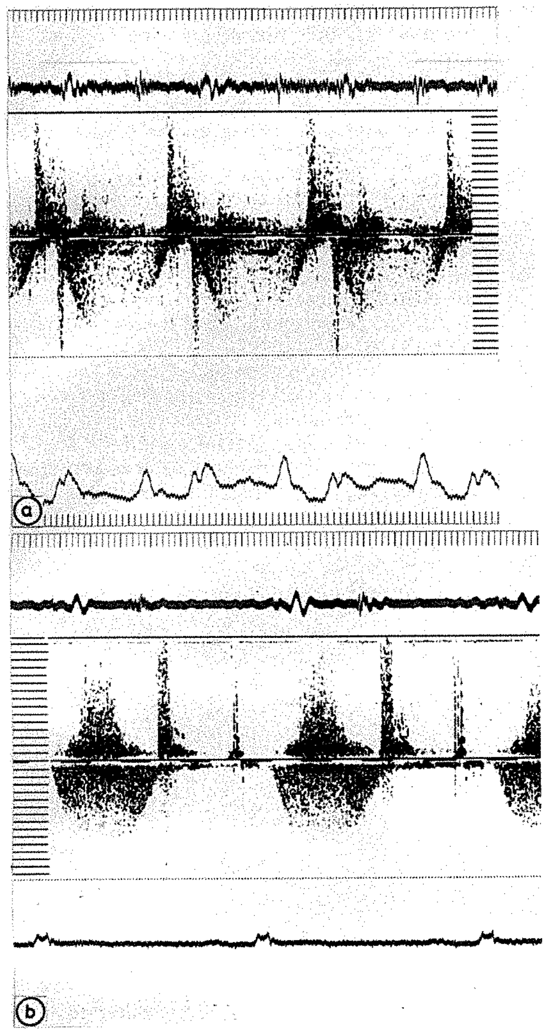


Fig 3 *(a) Continuous wave Doppler trace from a patient with sinus tachycardia, showing non-MR interval reduced to approximately 80 ms. (b) Continuous wave Doppler trace from the same patient while taking oral metoprolol. Heart rate has slowed and non-MR interval has increased to 400 ms. (Full scale deflection = 16 kHz).*

indeed limit cardiac output, it would be reasonable to treat it. One way would be to reduce the heart rate; such an action might explain the favourable response to β adrenoceptive blocking drugs seen in a minority of patients with dilated cardiomyopathy.[2] Figure 3 shows an example of such a patient who greatly improved with metroprolol as the filling time increased by a factor of more than three. The action of positive inotropic drugs in increasing the peak force of myocardial contraction and its peak rate of development is well recognised,[23] but their additional effect of shortening the overall duration of systole might be particularly valuable when filling time is limited and could perhaps be enhanced by suitable treatment design. A drug, such as digitalis, with both effects might thus have special advantages. Finally, the unexpected relation between retrograde mitral flow and motion of the valve cusps needs more study because the erosion of filling time by regurgitation that persists after mitral opening might also be manipulated by drugs.

The patients we have described all had a dilated cavity and a reduced ejection fraction; all might therefore have been diagnosed as having "heart failure" and a uniform treatment prescribed. However, the position of the rate limiting step in the circulation varied even in this small group. We believe that individual treatment on the basis of individual analysis of the underlying disturbance to the circulation may be a more fruitful approach to the management of the common but intractable clinical problem of advanced ventricular disease.

References

1 Braunwald E, Ross J Jr, Sonnenblick EH. Mechanisms of contraction in the normal and failing heart. *N Engl J Med* 1967;**277**:1012–22.

2 Swedberg K, Hjalmarson Å, Waagstein F, Wallentin I. Beneficial effects of long term beta-blockade in congestive cardiomyopathy. *Br Heart J* 1980;**44**:117–33.

3 Gibson DG, Brown D. Measurement of instantaneous left ventricular dimension and filling rate in man, using echocardiography. *Br Heart J* 1973;**35**:1141–9.

4 Mattheos M, Shapiro E, Oldershaw PJ, Sacchetti R, Gibson DG. Non-invasive assessment of changes in left ventricular relaxation by combined phono-, echo- and mechanography. *Br Heart J* 1982;**47**:253–60.

5 Oldershaw PJ, Dawkins KD, Ward DE, Gibson DG. Diastolic mechanisms of impaired exercise tolerance in aortic valve disease. *Br Heart J* 1983;**49**:568–73.

6 Lewis RP, Boudalas H, Forester WF, Weissler AM. A critical review of systolic time intervals. *Circulation* 1977;**56**:146–58.

7 Evans SJW, Mills P, Dawson J. The end of the p value? *Br Heart J* 1988;**60**:177–80.

8 Bland JM, Altman DG. Statistical methods for assessing agreement between two methods of clinical measurement. *Lancet* 1986;**i**:307–10.

9 Grossman W, McLaurin LP, Rolett EL. Alterations in left ventricular relaxation and diastolic compliance in congestive cardiomyopathy. *Cardiovasc Res* 1979; **13**:514–22.

10 Carroll JD, Lang RM, Neumann AL, Borow KM, Rajfer SI. The differential effect of positive inotropic and vasodilator therapy on diastolic properties in patients with congestive cardiomyopathy. *Circulation* 1986;**74**:815–25.

11 Rahko PS, Shaver JA, Salerni R, Uretsky BF. Digital

echocardiographic analysis of left ventricular filling in dilated cardiomyopathy. *Am J Noninvas Cardiol* 1988;**2**:10–8.

12 Hammermeister KE, Warbasse JR. The rate of change of left ventricular volume in man. II Diastolic events in health and disease. *Circulation* 1974;**49**:739–47.

13 Gibson DG. Assessment of ventricular diastolic function. In: Parmley WW, Chatterjee K, eds. *Cardiology*. Lippincott: Philadelphia, 1987:53:1–17.

14 Fioretti P, Brower RW, Meester GT, Serruys PW. Interaction of left ventricular relaxation and filling during early diastole in human subjects. *Am J Cardiol* 1980;**46**:197–203.

15 Hui WKK, Gibson DG. The dynamics of rapid left ventricular filling. *Adv Cardiol* 1985;**32**:7–35.

16 Gibson DG, Prewitt TA, Brown DJ. Analysis of left ventricular wall movement during isovolumic relaxation and its relation to coronary artery disease. *Br Heart J* 1976;**38**:1010–9.

17 Gibson DG, Brown DJ. Continuous assessment of left ventricular shape in man. *Br Heart J* 1975;**37**:904–10.

18 Brutsaert DL, Housmans PR, Goethals MA. Dual control of relaxation: its role in the ventricular function in the mammalian heart. *Circ Res* 1980;**47**:637–52.

19 Bristow MR, Ginsburg R, Minobe W, *et al.* Decreased catecholamine sensitivity and beta-adrenergic-receptor density in failing human hearts. *N Engl J Med* 1982;**307**:205–11.

20 Gwathmwey JK, Copelas L, MacKinnon R, *et al.* Abnormal intracellular calcium handling in myocardium from patients with end-stage heart failure. *Circ Res* 1987;**61**:70–6.

21 Gash AK, Carabello BA, Cepin D, Spann JF. Left ventricular ejection performance and systolic muscle function in patients with mitral stenosis. *Circulation* 1983;**67**:148–54.

22 Traill TA, St. John Sutton MG, Gibson DG. Mitral stenosis with high left ventricular diastolic pressure. *Br Heart J* 1979;**41**:405–11.

23 Sonnenblick EH, Braunwald E, Morrow AG. The contractile properties of human heart muscle: studies on myocardial mechanics of surgically excised papillary muscles. *J Clin Invest* 1965;**44**:966–77.

Br Heart J 1989;62:253–9

Influence of respiratory variations on right ventricular function

JOHN L CAPLIN, WILLIAM D FLATMAN,* LORRAINE DYKE,*
MARTIN N WISEMAN, DUNCAN S DYMOND

*From the Departments of Cardiology and *Nuclear Medicine, St Bartholomew's Hospital, London*

SUMMARY Respiratory effort during inspiration, expiration, and the Valsalva manoeuvre changes right ventricular preload and afterload. On inspiration these changes should improve systolic emptying of a larger end diastolic volume and so increase the ejection fraction, whereas on expiration the reverse should be true. The resting right ventricular ejection fraction was measured by first pass radionuclide angiography with gold-195m (half life 30·5 s) in 17 individuals at maximal inspiration and expiration and in eight at rest and during the strain phase (phase 2) of the Valsalva manoeuvre. The right ventricular ejection fraction was significantly lower during expiration than during inspiration. There were, however, no significant differences in bolus duration or right ventricular transit time. The Valsalva manoeuvre, in contrast, significantly increased the ejection fraction and also significantly prolonged both the bolus duration and right ventricular transit time. The conformation of the bolus curves during the Valsalva manoeuvre suggested the development of tricuspid regurgitation.

These data suggest that relative influences of venous return, pulmonary arterial pressure, pulmonary vascular resistance, and possible functional tricuspid regurgitation vary during inspiration, expiration, and the Valsava manoeuvre and can affect the right ventricular ejection fraction. Changes in right ventricular function on exercise assessed by first pass radionuclide angiography must be interpreted with caution because maximal respiratory effort may alter the right ventricular ejection fraction independently of ischaemia or other non-ischaemic factors.

Recognition of the importance of right ventricular function[1] has led to interest in its measurement. Radionuclide angiography is a safe, reproducible, and non-invasive method of assessing right ventricular ejection fraction.[2-5] When the first pass method is used right ventricular transit lasts only a few seconds, and so rapid changes in function can be assessed. The use of the ultrashort half life radiopharmaceutical gold-195m allows multiple, rapid, sequential first pass radionuclide angiograms to be performed with a low radiation burden.[6]

During inspiration the negative intrathoracic pressure draws blood into the right atrium and so increases right ventricular filling pressure.[7] In addition, the pulmonary vessels dilate as the lungs expand; thus pulmonary vascular impedance falls and this causes a fall in pulmonary artery pressure and hence right ventricular afterload.[8] In contrast during expiration right ventricular filling pressure falls and afterload increases. Since the right side of the heart is a low pressure system, these changes in preload and afterload during respiration might be expected to bring about relatively large changes in right ventricular systolic function. During inspiration right ventricular filling and emptying will be enhanced, and since the ejection fraction is a ratio of the stroke volume divided by the end diastolic volume, it should increase. The converse is true during expiration.

The Valsalva manoeuvre, forced expiration against pressure, reduced pulmonary flow and increased pulmonary arterial pressure.[9] An echocardiographic study suggested that right ventricular end diastolic volume falls during the Valsalva manoeuvre while stroke volume is maintained.[10] If these data are correct and the systolic function of the right ventricle is enhanced during the Valsalva manoeuvre, then

Requests for reprints to Dr John L Caplin, Cardiac Unit, Southampton General Hospital, Southampton SO9 4XY.

Accepted for publication 11 April 1989

because blood is not pumped forward, functional tricuspid regurgitation must be responsible for maintaining or increasing right ventricular ejection fraction.

This study was designed to investigate the respiratory changes in resting right ventricular function during maximal inspiration, expiration, and the Valsalva manoeuvre.

Patients and methods

PATIENTS

We studied 25 people (22 men). They had been referred to the nuclear cardiology laboratory for the assessment of resting ventricular function. Most had proven or suspected coronary artery disease, but some were assessed for the possibility of a left ventricular aneurysm or cardiomyopathy. We excluded those who were unable to lie flat or were not in sinus rhythm. None had a history of asthma or chronic sputum expectoration or clinical evidence of pulmonary disease. Chest radiography showed no pulmonary abnormality and no one was taking bronchodilator or steroid medication. Informed consent was obtained for the study. No adverse effects were noted during the study.

RADIONUCLIDE ANGIOGRAPHY

First pass radionuclide angiography was performed as previously described.[11] An 18 gauge cannula was inserted into a vein in the antecubital fossa and boluses of 15–20 mCi (550–750 MBq) of gold-195m were injected by a rapid saline flush. Details of the portable mercury-195m/gold-195m generator and its validation for use in man have already been described.[6 12] The subjects were imaged supine in the 30° right anterior oblique projection, which produces the best spatial separation of right atrium and right ventricle.[13]

INSPIRATION AND EXPIRATION

Before imaging the 17 subjects were instructed on taking and holding deep breaths, in and out. All subjects could hold their breath at maximal inspiration and expiration for at least 20 seconds. An initial injection was made to assess the time required for the bolus of radioactivity to pass through the circulation into the left ventricular phase, and the study proceeded only if this was less than 20 s. Subjects were then imaged at maximal inspiration and then at maximal expiration. The appropriate respiratory manoeuvre was held for the entire duration (20 s) of the first pass study, and imaging of the right ventricle was therefore not obtained during a change from inspiration to expiration or vice versa. Three minutes (>5 half lives) were allowed to elapse between each study.

REST AND VALSALVA MANOEUVRE

Eight subjects were instructed on how to perform a Valsalva manoeuvre (expiratory effort against a pressure) using a device specially designed to maintain an airway pressure of $\geqslant 35$ mm Hg (Medical Electronics Department, St Bartholomew's Hospital). All were able to maintain this pressure for at least 20 s. Radionuclide angiography was performed at rest and then during the holding of the strain phase (also known as phase 2) of the Valsalva manoeuvre.[14]

ANALYSIS OF DATA

Right ventricular ejection fraction was calculated by a manual, iterative technique from high frequency time-activity curves derived from a right ventricular region of interest.[15] An appropriate background correction was used.[16] Right ventricular images were derived from background corrected end systolic and end diastolic images. Bolus duration was measured from the full width at half maximum of a time-activity curve from a region of interest over the superior vena cava.[17] These curves were also analysed qualitatively for evidence of pulsatile flow, suggestive of tricuspid regurgitation (fig 1). A previous study showed that prolongation of the bolus has no significant effect upon the calculation of the right ventricular ejection fraction.[15] We derived the right ventricular transit time from the right ventricular time-activity curve, taking the first identified systolic frame (trough) as the beginning and the last diastolic frame (peak) as the end. The number of cycles available for analysis and the mean heart rate were also derived from the time-activity curve. Left ventricular function was not assessed because the left heart transit in first pass studies often came after the end of breath holding or the Valsalva manoeuvre (that is >20 s after the injection). Thus in some studies it was impossible to be certain at which phase of the respiratory cycle the left heart was imaged.

STATISTICAL ANALYSIS

Statistical analysis was performed with a commercially available software program on a microcomputer. Inspiratory and expiratory results were compared by paired *t* tests. Results are expressed as mean (SD).

Results

CHANGES FROM INSPIRATION TO EXPIRATION

Figure 2 shows the response of the right ventricular ejection fraction from maximal inspiration to expiration in all individuals. The right ventricular ejection fraction on inspiration ranged from 12 to 48% with a mean value of 31·8 (11·2)%. On expiration the range

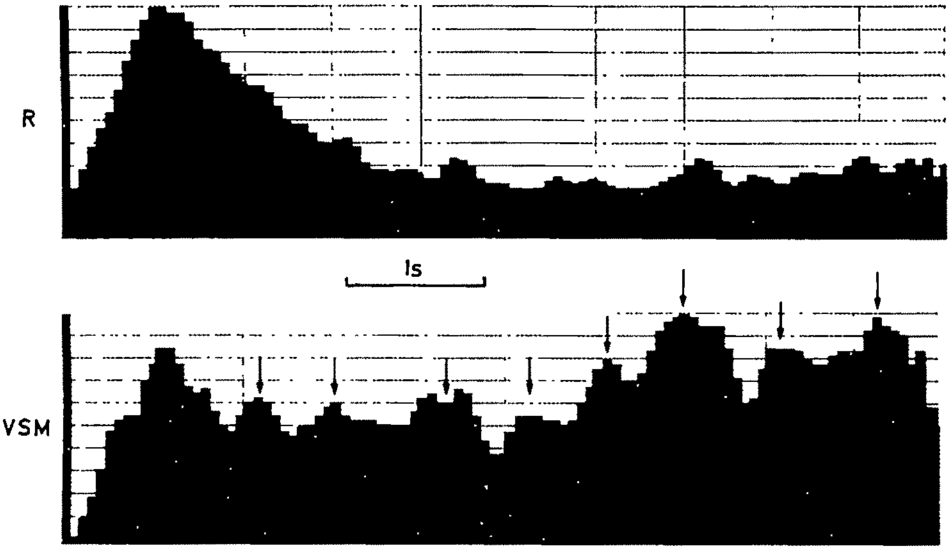


Fig 1 *Representative time-activity curves, with counts on the vertical axis and time on the horizontal axis, from a region of interest over the superior vena cava. Upper curve at rest and lower curve during Valsalva manoeuvre. Note the considerable prolongation of the bolus duration and the appearance of pulsatile events (arrows) during Valsalva manoeuvre R, rest, VSM, Valsalva manoeuvre.*

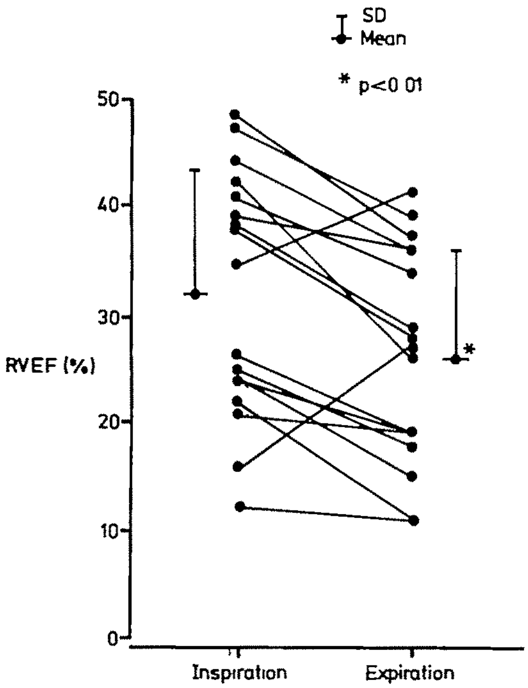


Fig 2 *Right ventricular ejection fractions on inspiration (left) and expiration in all 17 subjects (mean (SD)). RVEF, right ventricular ejection fraction.*

was 11–41% with a mean of 26·2 (9·9)% ($p < 0{\cdot}01$ *v* inspiration). In the whole group the change from inspiration to expiration was −5·7 (6·5)%. Fifteen of 17 individuals showed a fall in ejection fraction from inspiration to expiration ranging from 1 to 16%, with a mean 7·7 (3·8)%. Two subjects showed a rise of 6% and 11% respectively.

Figure 3 shows the distribution of changes in right ventricular ejection fraction from inspiration to expiration. This confirms that most individuals had a fall in ejection fraction, with a normal distribution around a median value of −7%. The 99% probability limits for the mean value are −10·3 to −1·1% indicating a high probability that these results represent a true fall in ejection fraction.

Table 1 shows the mean (SD) results for all individuals for the bolus duration, right ventricular ejection fraction, right ventricular cycles, right ventricular transit time, and heart rate. These are shown for inspiration, expiration, and the difference between these values. As shown in figure 2, there is a significant fall in ejection fraction, but there are no other significant differences.

CHANGES FROM REST TO THE VALSALVA MANOEUVRE

Figure 4 shows the change in right ventricular ejection fraction from rest to the Valsalva manoeuvre in eight subjects. The right ventricular ejection fraction increased from 29·4 (7·3)% (range 20–38%)

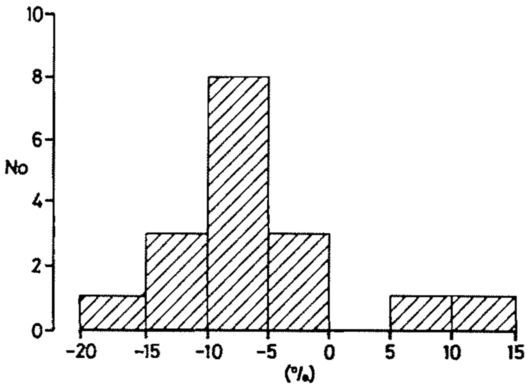


Fig 3 *Distribution of changes in right ventricular ejection fraction from inspiration to expiration.*

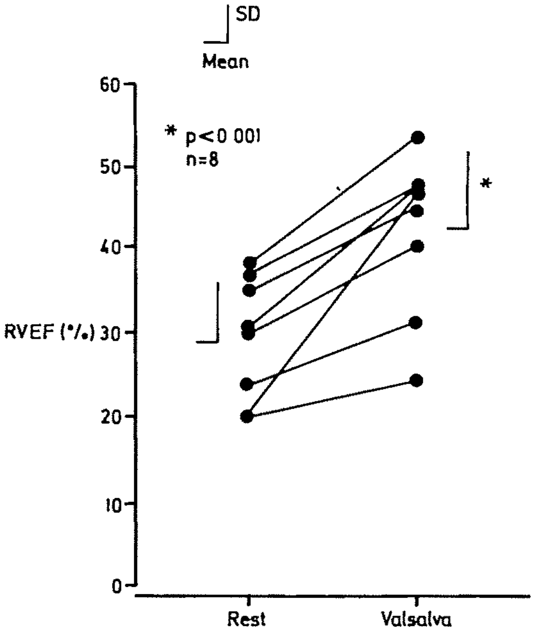


Fig 4 *Right ventricular ejection fraction at rest (left) and during Valsalva manoeuvre in all eight subjects (mean (SD)). RVEF, right ventricular ejection fraction.*

at rest to 42·6 (9·6)% (range 25–54%) during the Valsalva manoeuvre ($p < 0{\cdot}001$). All subjects showed a rise (mean 13·3 (6·8)%, range 5–27%).

Figure 5 shows the distribution of change in the ejection fraction from rest to Valsalva. The values are normally distributed around the mean.

Table 2 shows mean (SD) results in all the subjects of the bolus duration, right ventricular ejection fraction, right ventricular cycles, right ventricular transit time, and heart rate. In contrast with the inspiration/expiration results, bolus duration, right ventricular cycles, and right ventricular transit time were all significantly increased during the Valsalva manoeuvre. Heart rate was increased, and although this just fails to reach statistical significance it does suggest that imaging was performed during the strain phase of the Valsalva manoeuvre.[18]

Analysis of the changes in the bolus time-activity curve from rest to the Valsalva manoeuvre showed that six of the eight subjects had pronounced increases in bolus duration. In all these individuals pulsatile waves appeared during the Valsalva manoeuvre as shown in fig 1. These were caused by oscillation of the bolus of radionuclide in the superior vena cava at a rate similar to the heart rate. These are suggestive, although not diagnostic of the development of tricuspid reflux, and, in our experience, are not seen in any other condition. A hold up of the passage of bolus for any other cause is not associated with regular pulsatile changes in the time-activity curve.

Table 1 *Changes from inspiration to expiration (mean (SD))*

Variable	*Inspiration*	*Expiration*	*Difference*
Bolus duration (s)	1·3 (1·0)	1·5 (0·7)	0·1 (1·0)
RVEF (%)	31·8 (11·2)	26·2 (9·9)*	−5·7 (6·5)
RV cycles	5 (1·5)	5·8 (2·7)	0·8 (2·6)
RV transit time (s)	3·7 (1·3)	4·1 (1·8)	0·4 (1·8)
Heart rate (beats/min)	76·5 (12·8)	79·6 (13·1)	3·1 (6·5)

*$p < 0{\cdot}01$ inspiration *v* expiration. EF, ejection fraction; RV, right ventricular.

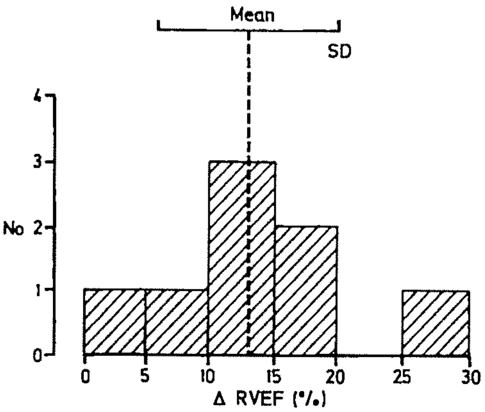


Fig 5 *Distribution of changes in right ventricular ejection fraction from rest to Valsalva manoeuvre. RVEF, right ventricular ejection fraction.*

Table 2 *Changes from rest to Valsalva manoeuvre (mean (SD))*

Variable	*Rest*	*Valsalva*	*Difference*
Bolus duration (s)	0·9 (0·2)	2·8 (1·8)*	1·9 (1·8)
RVEF (%)	29·4 (7·3)	42·6 (9·6)**	13·3 (6·8)
RV cycles	4·1 (1·0)	7·8 (4·0)*	3·6 (3·5)
RV transit time (s)	3·3 (0·9)	5·3 (2·3)*	2·0 (1·8)
Heart rate (beats/min)	67·1 (14·7)	81·8 (17·8)	14·6 (19·9)

*$p < 0·05$, **$p < 0·001$. Same abbreviations as table 1

Discussion

METHODS OF ASSESSING RESPIRATORY CHANGES IN RIGHT VENTRICULAR FUNCTION

Radionuclide angiography has several advantages over other methods of studying the right ventricle. It is non-invasive, does not induce arrhythmias and does not require assumptions about the right ventricle's complex geometric shape. In gated studies[2 4] overlap by other chambers may be a problem, and the time required for data acquisition means that rapid changes will be missed. It would be difficult, if not impossible, to perform gated studies to assess the respiratory changes in right ventricular function because of this. Echocardiography, although non-invasive and having good spatial resolution, has the inherent disadvantages that the assessment of changes in right ventricular volume requires both assumptions about ventricular shape and good imaging in at least two planes.[19 20] Since during respiration there is movement of the heart it is difficult to locate the same planes at different phases of the respiratory cycle. Thus first pass radionuclide angiography is uniquely suited to the study of rapid changes in right ventricular function, and the use of gold-195m means that multiple rapid studies may be performed with a low radiation burden.[21]

CHANGES WITH RESPIRATION

This study showed that right ventricular ejection fraction falls from maximal inspiration to expiration by, on average, about 6%. This is not unexpected because venous return, and therefore right ventricular preload, falls and afterload increases during expiration. The radionuclide assessment of right ventricular ejection fraction correlates well with haemodynamic measures of right ventricular function, particularly mean pulmonary artery pressure and to some extent right ventricular filling pressure.[22] But radionuclide angiography is sensitive enough to show the changes in right ventricular ejection fraction that accompany respiratory induced changes in haemodynamic function. Since the mean ejection fraction on inspiration was about 30%, a fall of about 6% represents an average overall 20% fall in ejection fraction. Impaired atrial filling and increased intrathoracic pressure on maximal expiration did not significantly prolong either the bolus duration or the right ventricular transit time.

CHANGES DURING THE VALSALVA MANOEUVRE

In the second part of the study we assessed the effects of the Valsalva manoeuvre on right ventricular function. The strain phase of the Valsalva manoeuvre caused a fall in left ventricular volume and ejection fraction.[18] Echocardiographic studies that use the right ventricular area, a measure that correlates well with right ventricular volume, have shown falls of up to 70% in right ventricular end diastolic volume, associated with maintenance of or only a slight reduction in stroke volume.[10] Since the ejection fraction is calculated from stroke volume divided by end diastolic volume this should increase during the Valsalva manoeuvre.

Our data suggest that this may well be so, because there was on average a 45% increase in right ventricular ejection fraction from rest to the Valsalva manoeuvre. In contrast with the study of inspiration and expiration there was significant prolongation of both inflow to the right ventricle, as measured by bolus duration, and right ventricular transit time. Qualitative assessment of the bolus curves from the superior vena cava showed them to have a pulsatile element that is characteristic of tricuspid regurgitation. It is difficult to be certain that this feature really did reflect tricuspid reflux because the increase in right ventricular pressure might simply result in bolus hold up. However, in our experience, it is unusual to see these pulsatile waves in individuals with raised right sided pressures, but they often occur in patients with tricuspid regurgitation. We have previously shown that prolongation of bolus duration in itself has no effect on the calculated right ventricular ejection fraction,[15] so that the changes we saw in right ventricular ejection fraction during the Valsalva manoeuvre are unlikely to be related to this variable. Using the first pass technique we were unable to assess right ventricular volume, but the finding of increased right ventricular ejection fractions combined with data suggesting reduced forward flow in the pulmonary artery,[9] indicates an explanation for the apparent paradox of tricuspid regurgitation associated with reduced right ventricular end diastolic volumes. Thus it may be that right ventricular ejection fraction increases during the Valsalva manoeuvre despite increased afterload and reduced end diastolic volume because blood is ejected into the venous system via a regurgitant tricuspid valve. This hypothesis would fit the observed data, but further study is required to quantify the extent of the tricuspid regurgitation.

Finally, is it possible that the changes in right ventricular ejection fraction might also, in part, be caused by changes in heart rate or contactility. Heart rate increased, but not significantly from rest to the Valsalva manoeuvre. Studies of the relation between heart rate and left ventricular ejection fraction showed that over the physiological range, changes in heart rate do not significantly affect ejection fraction, and above this range the direction of change in ejection fraction, a fall with increased heart rate, is in the opposite direction to the changes that we found during the Valsalva manoeuvre.[23] The change in heart rate in the current study was < 40 beats/min in all cases and it seems unlikely that heart rate alone would explain the difference in right ventricular ejection fraction from rest to the Valsalva manoeuvre. In addition the change in heart rate might reflect the change in inotropic state and hence contractility; but data from left ventricular studies again suggest that in the range of heart rates studied this is unlikely to be so.[24] It seems unlikely that the changes we saw in right ventricular ejection fraction are related to changes in heart rate or contractility; they are more likely to reflect changes in loading conditions.

CONCLUSIONS AND CLINICAL IMPLICATIONS

These data suggest that the right ventricular ejection fraction, derived from first pass radionuclide angiography, is a sensitive method of assessing changes in right ventricular function during respiratory manoeuvres, and that the ejection fraction falls on maximal expiration and rises during the strain phase of the Valsalva manoeuvre. The clinical implications of these findings are unclear, but they do suggest that changes in right ventricular ejection fraction at peak exercise may, in part, be related to respiration, since rapid deep breathing occurs during exercise. These data may explain why the response of right ventricular ejection fraction to exercise is the same in normal individuals and in those with coronary artery disease and pulmonary disease.[25-27] They also imply that changes in right ventricular function on exercise, assessed by first pass studies in individuals with coronary disease, may not simply reflect right ventricular ischaemia.[26] It could be that respiratory manoeuvres may be of use as a test of right ventricular "functional reserve" in the assessment of patients with isolated right ventricular myopathies and in those with overt pulmonary disease in whom exercise studies are difficult, but as yet there are no data on this aspect.

JLC was supported by the British Heart Foundation.

References

1 Cohn JN, Guiha NH, Broder MI, Limas CJ. Right ventricular infarction: clinical and haemodynamic features. *Am J Cardiol* 1974;33:209–44.

2 Maddahi J, Berman DS, Matsouka DT, *et al.* A new technique for assessing right ventricular ejection fraction using rapid multiple-gated equilibrium cardiac blood pool scintigraphy. *Circulation* 1979; 60:581–9.

3 Harolds JA, Grove RB, Bowen RD, Powers TA. Right ventricular function as assessed by two radionuclide techniques. *J Nucl Med* 1981;22:113–5.

4 Legrand V, Chevign M, Foulon J, Rigo P. Evaluation of right-ventricular function by gated blood pool scintigraphy. *J Nucl Med* 1983;24:886–93.

5 Hurwitz RA, Treves S, Kurac A. Right and left ventricular ejection fraction in paediatric patients with normal hearts: first pass radionuclide angiocardiography. *Am Heart J* 1983;107:726–32.

6 Dymond DS, Elliot AT, Flatman W, *et al.* Clinical validation of gold-195m: a new short half-life radiopharmaceutical for rapid sequential first-pass angiocardiography in man. *J Am Coll Cardiol* 1983;2: 85–92.

7 Schlant RC. Normal physiology of the cardiovascular system. In: Hurst JW, ed. *The heart*. New York: McGraw Hill, 1978:71–100.

8 Benza GC, Mantero O, Marzegalli M, Morbelli E, Rampulla C, Morpurgo M. Simultaneous right and left heart catheterization and transmural pressure in chronic obstructive lung disease. *Prog Resp Res* 1975;9:55–62.

9 Wilkinson PL, Stowe DF, Tyberg JV, Parmley WW. Pressure and flow changes during Valsalva-like manoeuvers in dogs following volume infusion. *Am J Physiol* 1977;233:H93–9.

10 Little WC, Barr WK, Crawford MH. Altered effect of the Valsalva manoeuver on left ventricular volume in patients with cardiomyopathy. *Circulation* 1985;71: 227–33.

11 Dymond DS, Jarritt PH, Britton KE, Spurrell RAJ. Detection of postinfarction left ventricular aneurysms by first pass radionuclide ventriculography using a multicrystal gamma camera. *Br Heart J* 1979;41: 68–78.

12 Elliot AT, Dymond DS, Stone DL, *et al.* A mercury-195m/gold-195m generator for use in first pass nuclear angiocardiography. *Phys Med Biol* 1983;28: 139–47.

13 Ferlinz J. Measurement of right ventricular volumes in man from single-plane cineangiograms. *Am Heart J* 1977;94:87–90.

14 Zema MJ, Restivo B, Sos T, Sniderman KW, Kline S. Left ventricular dysfunction—bedside Valsalva manoeuvre. *Br Heart J* 1980;44:560–9.

15 Caplin JL, Dymond DS, Flatman W, Camm AJ. The effect of bolus duration and injection rates on the measurement of right ventricular ejection fraction (RVEF) by first-pass radionuclide angiography (FPRA) using gold-195m [Abstract]. *Clin Sci* 1984; 67:42P.

16 Dymond DS, Grenier RP, Schmidt DH. Right

ventricular ejection fraction from first-pass radionuclide angiograms: comparison with contrast right ventriculography [Abstract]. *J Nucl Med* 1981; 22:P23.

17 Dymond DS, Elliot A, Stone D, Hendrix G, Spurrell R. Factors that affect the reproducibility of left ventricular function from first-pass radionuclide ventriculograms. *Circulation* 1982;**65**:311–22.

18 Brooker JZ, Alderman EL, Harrison DC. Alterations in left ventricular volumes induced by Valsalva manoeuvre. *Br Heart J* 1974;**36**:713–8.

19 Levine RA, Gibson TC, Aretz T, *et al.* Echocardiographic measurement of right ventricular volume. *Circulation* 1984;**69**:497–505.

20 Wann SL, Stickles KR, Bamrah VS, Gross CM. Digital processing of contrast echocardiograms: a new technique for measuring right ventricular ejection fraction. *Am J Cardiol* 1984;**53**:1164–8.

21 Dymond DS, Caplin JL, Flatman W, Burnett P, Banim S, Spurrell R. Temporal evolution of changes in left ventricular function induced by cold pressor stimulation. An assessment with radionuclide angiography and gold 195m. *Br Heart J* 1984;**51**.557–64.

22 Korr KS, Gandsman AJ, Winkler ML, Shulman RS, Bough EW. Haemodynamic correlates of right ventricular ejection fraction measured with gated radionuclide angiography. *Am J Cardiol* 1982;**49**: 71–7.

23 Ricci DR, Orlick AE, Alderman EL, Ingels NB, Daughters GT, Stinson EB. Influence of heart rate on left ventricular ejection fraction in human beings. *Am J Cardiol* 1979;**44**:447–51.

24 Ricci DR, Orlick AE, Alderman EL, *et al.* Role of tachycardia as an inotropic stimulus in man. *J Clin Invest* 1979;**63**:695–703.

25 Johnson LJ, McCarthy DM, Sciacca RR, Cannon PJ. Right ventricular ejection fraction in patients with coronary artery disease. *Circulation* 1979;**60**:1284–91.

26 Olvey SK, Reduto LA, Stevens PM, Deaton WJ, Miller RR. First pass radionuclide assessment of right and left ventricular ejection fraction in chronic pulmonary disease. *Chest* 1980;**78**:4–9.

27 Matthay RA, Berger HJ, Davies RA, *et al.* Right and left ventricular exercise performance in chronic obstructive pulmonary disease: radionuclide assessment. *Ann Intern Med* 1980;**93**:234–9.

Br Heart J 1989;62:260–7

Diagnosis of ventricular septal rupture after myocardial infarction: value of colour flow mapping

JOHN SMYLLIE,* KEITH DAWKINS, NEVILLE CONWAY, GEORGE R SUTHERLAND*

From the Wessex Cardiothoracic Unit, Southampton General Hospital, Southampton

SUMMARY Twenty patients with ventricular septal rupture after myocardial infarction were investigated by cross sectional echocardiography with integrated pulsed and continuous wave Doppler and colour flow mapping. Confirmatory cardiac catheterisation was performed in 12 patients. Eighteen patients had surgical repair with inspection of the defect. Six patients in whom recurrent ventricular septal rupture developed were also investigated by Doppler echocardiography and colour flow mapping. Cross sectional echocardiography correctly predicted the infarct territory in all cases but visualised the septal rupture in only seven (35%). Pulsed and continuous wave Doppler detected a disturbance of right ventricular systolic flow that was diagnostic of a ventricular septal rupture in 19 (95%), but this only accurately predicted the site in 14 (70%). Colour flow mapping studies showed a mosaic jet traversing the interventricular septum in all 20 cases, and this accurately predicted the site of rupture. In addition colour flow mapping defined three sites of ventricular septal rupture: apical, posterior, and anterior trabecular. Five of the six patients with recurrent rupture were correctly diagnosed by pulsed and continuous wave Doppler and all six were diagnosed by colour flow mapping.

Cross sectional echocardiography with colour flow mapping is a highly sensitive and rapid technique for the assessment of postinfarction ventricular septal rupture before and after operation. It was more informative about the site of the rupture than pulsed and continuous wave Doppler echocardiography.

Ventricular septal rupture occurs in about 2% of patients with acute myocardial infarction.[1] Conservative treatment is associated with a high mortality[2] and therefore a rapid and accurate diagnosis is essential so that early surgical repair can be performed.[3-6] Because it is often difficult to distinguish between post-infarction ventricular septal rupture and acute mitral regurgitation on clinical grounds,[7] a rapid and reliable non-invasive diagnostic technique such as cardiac ultrasound is needed. Cross sectional echocardiography alone, however, may fail to visualise the defect in a considerable number of patients.[8-12] The addition of pulsed Doppler echocardiography increased the overall diagnostic accuracy but it was less sensitive in predicting the rupture site.[9-12] Colour flow mapping has been used in the diagnosis of post-infarction ventricular septal rupture,[13] but there are no published reports of studies to evaluate the potential benefits of colour flow mapping in the diagnosis and management of this condition.

We studied the diagnostic accuracy of all these ultrasound techniques in a group of patients with post-infarction ventricular septal rupture.

Patients and methods

PATIENTS

Between December 1986 and November 1987 all 20 patients referred to the Wessex Regional Cardiothoracic Unit with suspected post-infarction ventricular septal rupture were investigated by cross sectional echocardiography with integrated pulsed and continuous wave Doppler and colour flow mapping. Patients with isolated acute mitral regurgitation were excluded. The diagnosis was confirmed at operation (18 patients) or necropsy (two patients).

There were 13 men and seven women (aged 52–78

Requests for reprints to Dr George R Sutherland, Department of Echocardiography, Thoraxcentre, Dijkzigt Academic Hospital, 3000-DR Rotterdam, The Netherlands.

*Present address: Thoraxcentre, Rotterdam, The Netherlands

Accepted for publication 26 April 1989

Table 1 *Clinical and surgical data of 20 patients with post-infarct ventricular septal rupture (VSR)*

General.		
Mean age	68	(range 52–78) yr
Male.female	1 9:1	
Anterior infarction	11	(55%)
Inferior infarction	9	(45%)
Mean time from infarct to VSR	3	(range 0–16) days
Diagnostic techniques:		
CS echo, Doppler, and CFM	20	
Cardiac catheterisation	12	
Surgical:		
VSR closure alone	12	
With associated LV aneurysm resection	2	
With associated coronary grafts	6	
No operation	2	
Early death	1	(5%)
Recurrent VSRs	6	(33%)
Recurrent VSRs requiring reoperation	4	(22%)

CS echo, cross sectional echocardiography; CFM, colour flow mapping; LV, left ventricular

(mean 68) years) (table 1). Eleven had sustained an anterior myocardial infarct and nine an inferior myocardial infarct as judged by a 12 lead electrocardiogram. Eighteen patients underwent closure of the ventricular septal rupture, two with associated left ventricular aneurysm resection and six with additional coronary artery bypass grafts. Two patients did not proceed to operation because of coexisting medical conditions; both died within days of diagnosis. In six patients (33%) recurrent ventricular septal rupture developed; these were confirmed by cardiac catheterisation, Doppler echocardiography, or both and only four (22%) required reoperation on clinical criteria.

METHODS

Echocardiography

All echocardiographic studies were performed at the bedside immediately the patient arrived on the unit and were completed within 25 minutes. Cross sectional echocardiography with integrated pulsed and continuous wave Doppler and colour flow mapping studies were performed with a Toshiba SSH 65A. Standard parasternal, apical, and subcostal views were examined in all patients. When the ventricular septal rupture was visualised the pulsed Doppler sample was placed in the right ventricle, adjacent to the exit point of the defect, in order to detect the abnormal right ventricular systolic turbulence that is diagnostic of a ventricular septal defect.[14] The continuous wave Doppler beam was then aligned across the defect to obtain the clearest maximal systolic velocity contour and to assess both the systolic and diastolic shunting patterns. If the ventricular septal rupture was not visualised the pulsed Doppler sample was placed at the right ventricular apex and moved down the interventricular septum in the apical four chamber view until systolic turbulence was detected. This latter manoeuvre was carried out in an attempt to define the area(s) of transmyocardial flow and thus predict the defect site. We performed the colour flow mapping studies using the velocity mode with the appropriate filter and gain settings after the initial imaging and Doppler studies. The interventricular septum was then imaged, as before, until a mosaic jet signifying high velocity turbulent flow was identified traversing the septum. The position of the defect and the number of jets arising from the same defect or multiple defects were then noted. Mitral regurgitation if present was identified by continuous wave Doppler and colour flow mapping.

The same protocol was applied to postoperative patients with a suspected recurrence of a ventricular septal rupture.

Cardiac catheterisation

Left ventricular cineangiography and selective coronary arteriography were performed in 12 patients, and three had additional right heart catheterisation. Four of the six patients with recurrent defects had both left and right heart catheterisation.

Results

CROSS SECTIONAL ECHOCARDIOGRAPHY

Wall motion

Cross sectional echocardiography correctly identified the infarct territory in all 20 patients by identifying areas of abnormal wall thinning and wall motion, and this correlated with the electrocardiogram and the left ventricular cineangiogram. Six of the 11 anterior myocardial infarcts had obvious dyskinetic segments with a characteristic bulge of the apical septum protruding into the right ventricle.

Visualisation of the ventricular septal rupture

The ventricular septal rupture was directly visualised in seven patients (35%) (table 2). In the remaining 13 patients complete interruption of the interventricular septum could not be demonstrated. In several patients there were localised areas of abnormal septal motion or septal thinning which, although suspicious, were not considered diagnostic of post-infarction ventricular septal rupture.

PULSED AND CONTINUOUS WAVE DOPPLER

Abnormal right ventricular flow disturbance

Pulsed Doppler echocardiography detected an abnormal right ventricular systolic flow, characteristic of a ventricular septal defect, in 19 patients (95%)

P. 25 740

Table 2 *Diagnostic accuracy of each echocardiographic technique in 20 patients with post-infarction ventricular septal rupture*

	CS echo alone	*PW and CW Doppler*	*Colour flow mapping*
Correct diagnosis	7 (35%)	19 (95%)	20 (100%)
Accurate site prediction	7 (35%)	14 (70%)	20 (100%)

CS echo, cross sectional echocardiography; PW and CW, pulsed and continuous wave Doppler echocardiography.

(table 2). This systolic flow disturbance was of high velocity in all the cases studied and resulted in an aliased pulsed Doppler signal. Continuous wave Doppler also detected a high velocity jet in 95%, with peak velocities ranging from 1·9 to 4·0 m/s. Pulsed and continuous wave Doppler were non-diagnostic in an obese patient who was very ill.

Doppler evaluation of the site of ventricular septal rupture

In 14 patients (70%) pulsed Doppler correctly estimated the position of the ventricular septal rupture found by inspection of the defect at operation or necropsy (table 2). In the remaining six patients it did not. One patient had no detectable abnormal Doppler signal diagnostic of a post-infarction ventricular septal defect (see above). The other five patients were thought to have apical defects on the basis of the Doppler signal alone; however, at surgical inspection two had posterior and three had anterior trabecular ventricular septal rupture.

Systolic and diastolic shunting patterns

Systolic left to right ventricular shunting was shown in 19 patients by continuous wave Doppler. This typically resulted in a high velocity, systolic jet directed towards the transducer (fig 1). In six

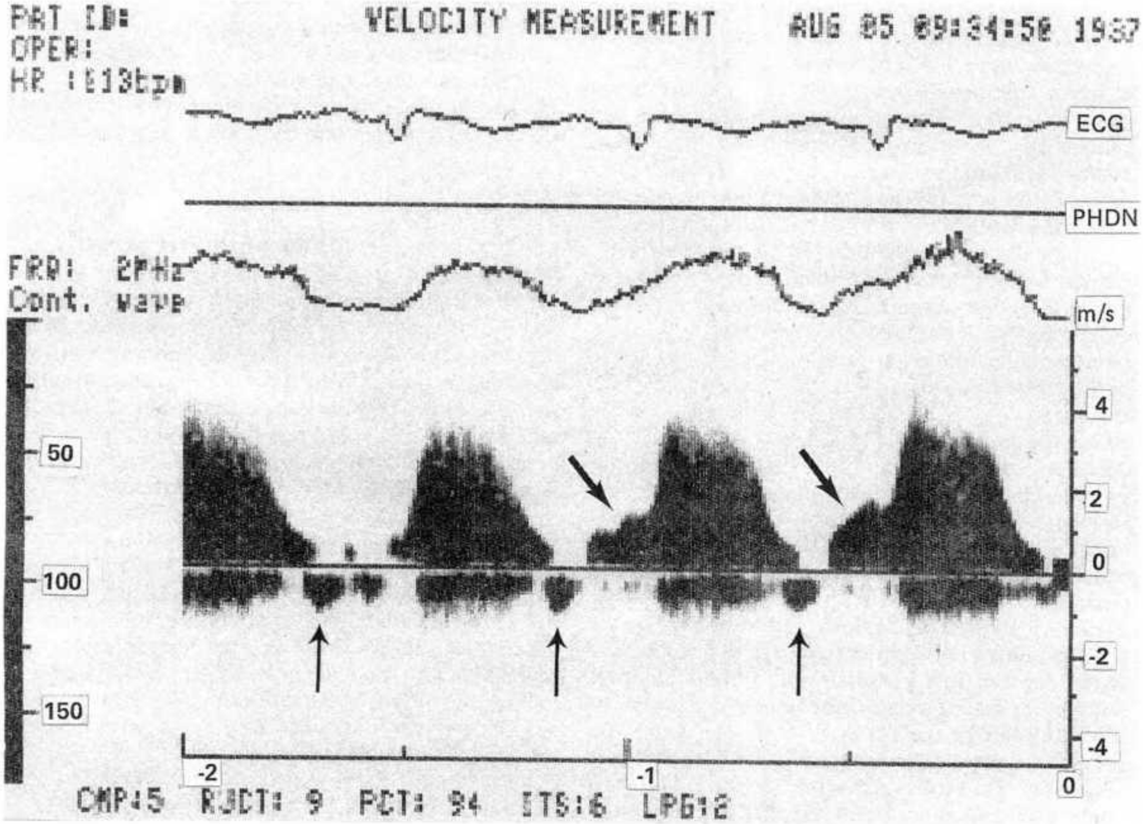


Fig 1 *A continuous wave Doppler echocardiogram recording from a patient with a post-infarction ventricular septal rupture showing high velocity (3·8 m/s) systolic left to right shunting. In diastole there was almost pandiastolic left to right shunting (thick arrows) with a characteristic rise in velocity towards the end of diastole. In early diastole there was a short period of flow reversal (thin arrows) which is of low velocity and indicates right to left shunting (see text).*

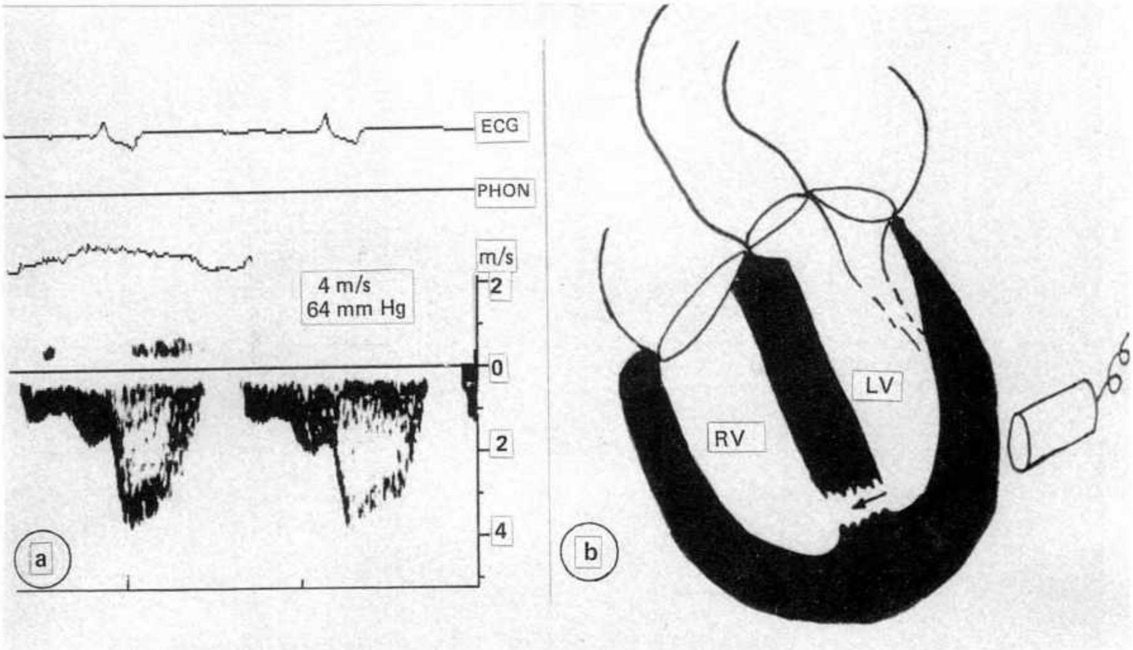


Fig 2 *(a) A continuous wave Doppler echocardiogram recording and (b) a diagram from a patient with an apical post-infarction ventricular septal rupture. The continuous wave recording (a) has a negative Doppler shift indicating flow directed away from the transducer. The peak systolic velocity is 4·0 m/s. The diagram (b) represents the alignment of the continuous wave transducer to the apical defect and shows how flow from the left to the right ventricle may be directed away from a precordial transducer when it is placed at the apex.*

patients, however, a high velocity systolic waveform directed away from the transducer was recorded (fig 2a). This occurred in apical and anterior trabecular post-infarction ventricular septal rupture and only when the transducer was placed at the apex (fig 2b). This negative waveform closely resembled that of tricuspid regurgitation with which it could easily be confused.

Diastolic left to right ventricular shunting was detected in 15 patients. This was almost pandiastolic and of much lower velocity than the systolic shunt, with a characteristic increase in velocity towards the end of diastole (fig 1, thick arrows). In eight patients continuous wave Doppler showed a reversal of flow in early diastole, indicating a short period of right to left shunting (fig 1, thin arrows). In two of these patients, simultaneous dual catheter studies indicated a "crossover" of left and right ventricular pressures during the period of isovolumic relaxation.

COLOUR FLOW MAPPING

Colour flow mapping detected one or more mosaic jets (indicating high velocity, turbulent flow) traversing the interventricular septum in all 20 patients. Demonstration of colour encoded transseptal flow and the exit point of the defect accurately predicted the site of the defect and this site correlated with what was found at operation (table 2). Multiple jets were seen in three patients; they arose from the same defect in two and from two separate defects in the other. In addition colour flow mapping recognised three separate areas of flow disturbance within the interventricular septum—apical (six patients), posterior (nine patients), and anterior trabecular (five patients)—each diagnostic of a specific rupture site. Figures 3–5 show examples of these different flow patterns. In fig 3, there is a broad mosaic jet traversing the interventricular septum, passing from the left to the right ventricle that represents a large apical ventricular septal rupture. In fig 4, two mosaic jets arise from the same defect and represent a fenestrated posterior ventricular septal defect, which was confirmed at operation. In fig 5, two mosaic jets seem to originate from a single anterior trabecular defect, with one jet directed towards the apex and the other jet back towards the tricuspid valve. This was caused by a muscle band that lay across the septal surface of the right ventricular exit point of the defect and split the ventricular septal defect jet into two.

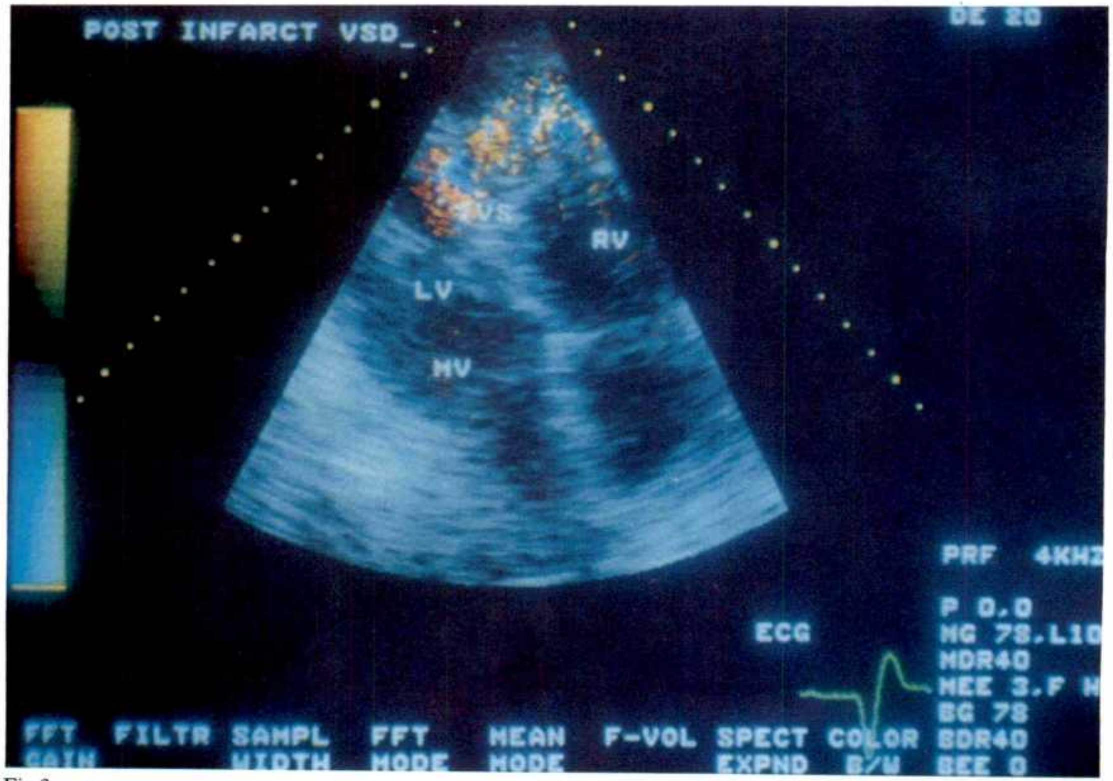

POST INFARCT VSD_
DE 20
IVS
RV
LV
MV
PRF 4KH
P 0.0
MG 78.L1
MDR40
MEE 3.F H
BG 78
BDR40
BEE 0
ECG
FFT GAIN
FILTR
SAMPL WIDTH
FFT MODE
MEAN MODE
F-VOL
SPECT EXPND
COLOR B/W

Fig 3

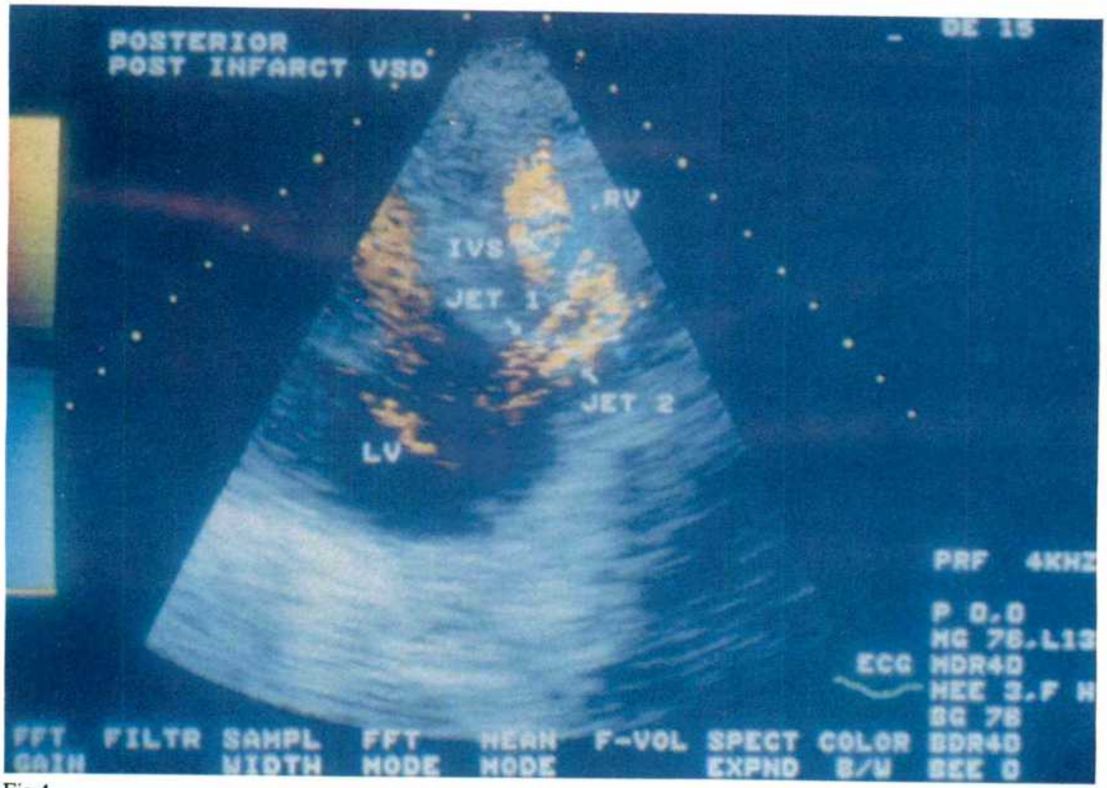

POSTERIOR
POST INFARCT VSD
DE 15
RV
IVS
JET 1
JET 2
LV
PRF 4KH
P 0.0
MG 78.L1
ECG
MDR40
MEE 3.F H
BG 78
BDR40
BEE 0
FFT GAIN
FILTR
SAMPL WIDTH
FFT MODE
MEAN MODE
F-VOL
SPECT EXPND
COLOR B/W

Fig 4

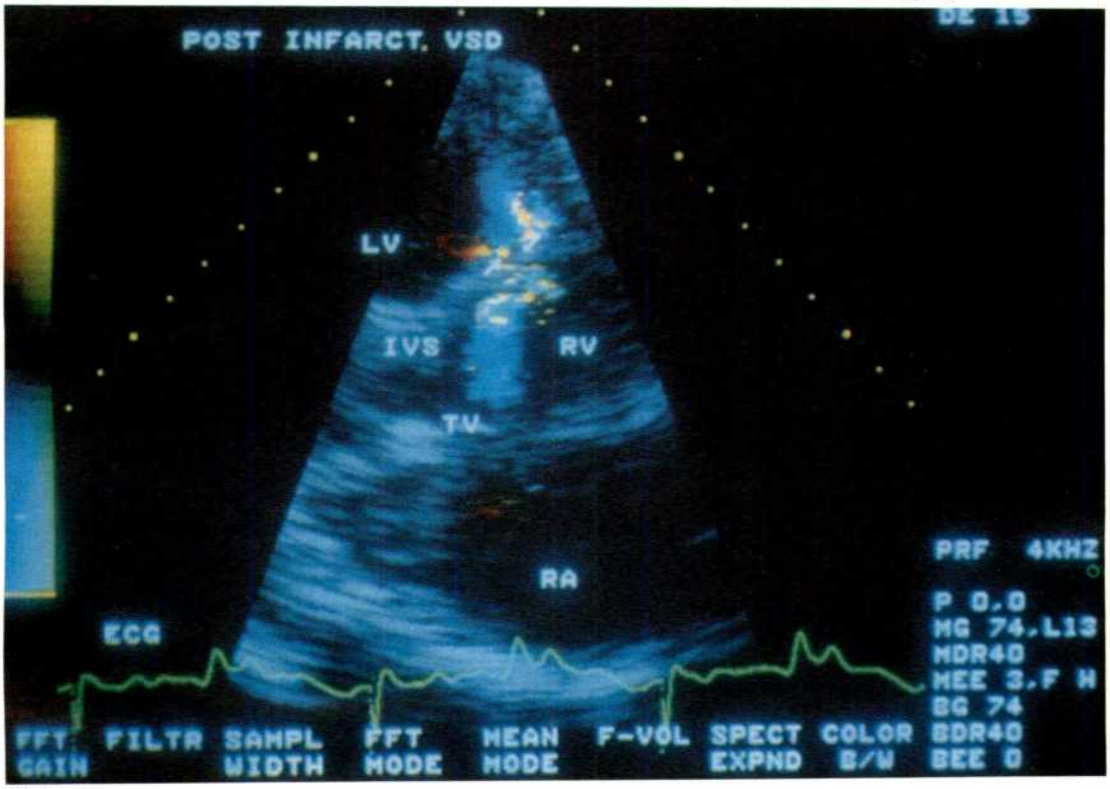


Fig 5

Fig 3 *Colour flow map recorded in the apical four chamber view during systole showing an apical post-infarction ventricular septal rupture (mosaic jet) traversing the apical septum (see text). LV, left ventricle; RV, right ventricle; IVS, interventricular septum; MV, mitral valve; TV, tricuspid valve; RA, right atrium.*

Fig 4 *Colour flow map recorded from the apex with the transducer tilted to image the posterior septum during systole. This shows a posterior ventricular septal rupture (see text). See fig 3 for abbreviations.*

Fig 5 *Colour flow map recorded in a modified four chamber view during systole. This shows an anterior trabecular rupture (see text). See fig 3 for abbreviations.*

Recurrent ventricular septal rupture (see table 3)
Recurrent ventricular septal rupture developed in six patients out of the 18 who underwent surgical repair (33%). This was shown by colour flow mapping studies. In four patients the diagnosis was confirmed by cardiac catheterisation and reoperation. Cross sectional echocardiography detected the presence of only one recurrent ventricular septal rupture. Pulsed Doppler was accurate in five patients and colour flow mapping was accurate in all six. In one patient colour flow mapping detected two separate ventricular septal defect jets, one at the lower end of the patch suggesting patch dehiscence and the other away from the patch suggesting further septal rupture—this was later confirmed at operation.

Table 3 *Diagnostic accuracy of each echocardiographic technique in the six patients with recurrent ventricular septal rupture*

	CS echo alone	*PW and CW Doppler*	*Colour flow mapping*
Correct diagnosis	1 (17%)	5 (83%)	6 (100%)
Accurate site prediction	1 (17%)	4 (67%)	6 (100%)

See table 2 for abbreviations.

Discussion

The results from this study suggest that colour flow mapping is both a rapid and sensitive technique for the diagnosis and preoperative assessment of patients with post-infarction ventricular septal rupture. It also gave more information than conventional imaging and Doppler. In this series cross sectional echocardiography failed to image >50% of defects, and this finding accords with previously reported series.[8-12] The addition of pulsed Doppler increased the overall diagnostic yield but was not accurate in predicting precisely the defect site. In many patients, colour flow mapping showed a widespread disturbance of right ventricular flow and this might explain the difficulties in detecting the precise right ventricular exit point of the ventricular septal defect by pulsed Doppler. Pulsed Doppler studies were also time consuming and required a more rigorous examination technique than colour flow mapping studies.

Colour flow mapping was also able to show multiple ventricular septal defect jets, which was not possible by conventional pulsed Doppler. In this study four patients had multiple jets (three new and one recurrent). Two of these patients had jets arising from different areas of the septum and so the diagnosis of multiple defects was obvious. In the other two patients the colour jets originated from the same area of the septum and so a definitive diagnosis of multiple defects was not possible. None the less, the knowledge that multiple defects were in close proximity was of practical value to the surgeon.

Three differing, discrete, areas of transseptal flow could be identified by colour flow mapping. Correlation with the findings at operation showed these to be diagnostic of apical, anterior trabecular, or posterior ventricular septal defects (figs 3–5). Apical jets represented defects confined to the apical septum, anterior trabecular jets represented defects confined to the central and anterior septum, and posterior jets represented muscular defects in the inlet septum. This classification of the site of post-infarction ventricular septal rupture flow by colour flow mapping was easily recognisable and understood, and correlated well with the findings at operation.

To date there are little published data on the use of continuous wave Doppler in the assessment of post-infarction ventricular septal rupture. The results from this study suggest that continuous wave Doppler can be used to detect and define the high velocity right ventricular flow disturbance associated with these defects. But when it is used alone confusion may arise with the recording of the velocity waveform from apical defects where a negative waveform may be obtained (fig 2a). This contrasts with both congenital defects and other forms of post-infarction ventricular septal rupture where a positive waveform is obtained. The unwary may confuse this negative waveform with tricuspid regurgitation, which produces a similar signal. In our experience the combined use of continuous wave Doppler with colour flow mapping overcame this problem because it showed the alignment of the continuous wave beam to specific areas of colour encoded transseptal flow.

The diastolic shunting patterns associated with post-infarction ventricular septal rupture are also defined by continuous wave Doppler. Left to right ventricular shunting from early to late diastole has been well described in both congenital restrictive and post-infarction ventricular septal rupture.[15] Early diastolic right to left shunting as shown by continuous wave Doppler has not been described before. This reversal of flow occupied a short period in early diastole that corresponded with the period of isovolumic relaxation. A postulated cause might be that a delay in right ventricular emptying would cause a crossover of left and right ventricular pressures so that the pressure in the right ventricle exceeded that of the left ventricle during this short period in early diastole. Although this early reversal of diastolic flow was of low velocity and its haemodynamic importance uncertain, it could explain the mechanism of positive contrast echocardiography, where a peripheral intravenous injection of microbubbles appears to cross from the right to the left ventricle.[8]

Colour flow mapping also proved more valuable than pulsed Doppler in the postoperative period for the assessment of patients in whom recurrent ventricular septal rupture developed. Pulsed Doppler missed the diagnosis in one patient who had coexisting mitral regurgitation. Later a diagnosis based on colour flow mapping was correct. Colour flow mapping was not only highly accurate, but in one patient distinguished between patch dehiscence and further septal rupture. This was not possible with the conventional Doppler techniques.

The role of left heart catheterisation (in particular left ventricular cineangiography) in the management of post-infarction ventricular septal rupture has been questioned.[11 12] But the insensitivity of pulsed Doppler in predicting the site of the defect has led to left ventricular cineangiography being regarded as a necessary aid to operation. Colour flow mapping has now reduced the need for left ventricular cineangiography; not only is it quicker and more sensitive but it carries less risk.[3] Left ventricular cineangiography is no longer routinely used in our unit for the preoperative assessment of post-infarction ventricular septal rupture. The role of coronary arteriography is perhaps more contentious and is outside the scope of this paper, but the initial impression from this study was that post-infarction ventricular septal rupture caused by anterior infarcts was associated with a different distribution of coronary disease than that caused by inferior infarcts—anterior infarcts were often associated with single vessel disease whereas inferior infarcts were more frequently associated with multiple vessel disease.

In our opinion, colour flow mapping is the best technique for the diagnosis and the preoperative and postoperative assessment of post-infarction ventricular septal rupture. It supersedes conventional pulsed Doppler echocardiography and left ventricular cineangiography, and may obviate the need for any invasive investigation in selected cases.

References

1 Moore CA, Nygaard TW, Kaiser DL, Cooper AA, Gibson RS. Postinfarction ventricular septal defect: the importance of location of infarction and right ventricular function in determining survival. *Circulation* 1986;74:45–55.

2 Sanders R, Kern W, Blount S. Perforation of the intraventricular septum complicating myocardial infarction. A report of 8 cases, one with cardiac catheterisation. *Am Heart J* 1956;51:736–48.

3 Kaplan MA, Harris CN, Kay JH, Parker DP, Magidson O. Postinfarction ventricular septal rupture. Clinical approach and surgical results. *Chest* 1976;69:734–8.

4 Gaudiani VA, Miller DC, Stinson EB, *et al.* Postinfarction ventricular septal defect. An argument for early operation. *Surgery* 1981;89:48–55.

5 Keenan DJ, Monro JL, Ross JK, Manners JM, Conway N, Johnson AM. Acquired ventricular septal defect. *J Thorac Cardiovasc Surg* 1983;85:116–9.

6 Norell MS, Gershlick AH, Pillai R, *et al.* Ventricular septal rupture complicating myocardial infarction: is early surgery justified? *Eur Heart J* 1987;8:1281–6.

7 Dougall JC, Pryor R, Blant SG. Systolic murmur following myocardial infarction. *Am Heart J* 1974;87:577–83.

8 Drobac M, Gilbert B, Howard R, Baigrie R, Rakowski H. Ventricular septal defect after myocardial infarction: diagnosis by two-dimensional contrast echocardiography. *Circulation* 1983;67:335–41.

9 Recusani F, Raisaro A, Sgalambro A, *et al.* Ventricular septal rupture after myocardial infarction: diagnosis by two-dimensional and pulsed Doppler echocardiography. *Am J Cardiol* 1984;54:277–81.

10 Miyatake K, Okamoto M, Kinoshita N, *et al.* Doppler echocardiographic features of ventricular septal rupture in myocardial infarction. *J Am Coll Cardiol* 1985;5:182–7.

11 Smith G, Endresen K, Sivertssen E, Semb G. Ventricular septal rupture diagnosed by simultaneous cross sectional echocardiography and pulsed Doppler ultrasound. *Eur Heart J* 1985;6:631–6.

12 MacLeod D, Fananapazir L, de Bono D, Bloomfield P. Ventricular septal defect after myocardial infarction: assessment by cross sectional echocardiography with pulsed wave Doppler scanning. *Br Heart J* 1987;58:214–7.

13 Zachariah ZP, Hsiung MC, Nanda NC, Camarano GP. Diagnosis of rupture of the ventricular septum during acute myocardial infarction by Doppler color flow mapping. *Am J Cardiol* 1987;59:162–3.

14 Stevenson JG, Kawabori I, Dooley T, Guntheroth WG. Diagnosis of ventricular septal defect by pulsed Doppler echocardiography. Sensitivity, specificity and limitations. *Circulation* 1978;58:322–6.

15 Hatle L, Angelsen B. *Doppler ultrasound in cardiology: physical principles and clinical application.* Philadelphia: Lea and Febiger, 1985:236.

Br Heart J 1989;62:268–72

Patterns of coronary artery disease in post-infarction ventricular septal rupture

J D SKEHAN,* CATHERINE CAREY,* M S NORRELL,† M DE BELDER,*
R BALCON,† P G MILLS*

From The London Hospital, Whitechapel and †The London Chest Hospital, London

SUMMARY Cardiac angiography was reviewed in 91 patients with post-infarction ventricular septal rupture. The results were compared with those of 123 stable survivors who had a positive submaximal exercise test early after infarction. Anterior infarction and occlusion of the infarct vessel were more common in those with ventricular septal rupture than in the comparison group. In the group with ventricular septal rupture there was more left ventricular damage, with aneurysm formation in two thirds, and coronary angiography showed more single than triple vessel disease. In the comparison group there was more triple vessel disease than single vessel disease. Angiographically demonstrable collaterals to the infarct territory were not seen or only very faintly seen in 82% of those with septal rupture. Well developed collaterals were seen in two thirds of the comparison group.

These patterns of coronary disease suggest that ventricular septal rupture is more likely in patients with coronary occlusion and little or no collateral support to the infarct territory.

The interventricular septum is believed to rupture in approximately 1% of survivors of myocardial infarction.[1] Early investigation and operation are the usual treatment.[2-4] This study was prompted by the clinical impression that we were seeing consistent patterns of coronary collateral circulation and left ventricular anatomy in patients with post-infarction septal rupture.

It is difficult to find an appropriate control group in an observational study. Differences in patient selection, angiographic assessment, and intervals from infarction to investigation often make comparison with other published trials inappropriate. We overcame some of these problems by using a large well defined consecutive series of stable survivors of infarction as a comparison group.[5] We selected patients from the London and Newham hospitals who had an early post-infarction exercise test. This was followed by early coronary and left ventricular angiography. So the comparison group showed the angiographic features seen by us soon after infarction and this allowed direct comparison with the features we found in patients with septal rupture.

Patients and methods

PATIENTS

Ventricular septal rupture after myocardial infarction
We included all 91 patients seen from 1979 to 1987 at the London Hospital and London Chest Hospital with post-infarction septal rupture in whom cardiac cineangiograms were available.

Comparison group
A consecutive series of stable survivors of infarction aged <65 years underwent submaximal exercise testing at a mean interval of 12 days after infarction. A positive result was based on ischaemic changes on the electrocardiogram, angina, an abnormal blood pressure response, the development of ventricular arrhythmias, or inability to complete the protocol. Left ventricular and coronary angiography was performed on all 123 patients in this comparison group.

ANGIOGRAPHIC STUDY

Extent of coronary disease
The severity of coronary disease was assessed in at least two, and usually six projections by independent observers. Arterial occlusion or important stenosis (luminal diameter reduced by 70% or more) was assessed in the infarct and in the non-infarct related vessels.

Requests for reprints to Dr J D Skehan, Cardiac Department, The London Hospital, Whitechapel, London E1 1BB

Accepted for publication 2 May 1989

Table *Characteristics of patients with acquired ventricular septal rupture after myocardial infarction and a comparison group who had a positive submaximal exercise test soon after infarction*

	Ventricular septal rupture after myocardial infarction (n = 91)	*Early positive exercise test after myocardial infarction (n = 123)*
Mean age (yr) (SD)	63 (7 7)	54 (7 1)
Male:female ratio	2:1	5 1
Anterior infarct (%)	70	40
Infarct vessel occluded (%)	92	79
Median time (days) from infarct to catheter (range)	12 (1–470)	21 (7–40)
Aneurysm present (%)	66	24
Regional wall motion score	28	22

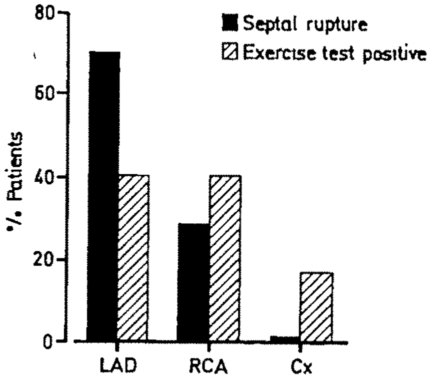


Fig 1 *Infarct vessel at angiography in patients with septal rupture and in the comparison group with a positive submaximal exercise test after infarction. LAD, left anterior descending coronary artery; RCA, right coronary artery; Cx, circumflex.*

Collateral circulation

Cross filling collateral circulation to the infarct related artery was assessed by a simple scoring system indicating flow from other vessels, whether dominant or non-dominant: 0, no collateral circulation; 1, faint filling of branch vessels; 2, faint filling of epicardial vessel; 3, good filling of epicardial vessel.

Left ventricular function

We used the system adopted by the Coronary Artery Surgery Study investigators to score regional wall motion and so estimate left ventricular function.[6] The left ventricular angiograms in both right and left anterior oblique projections were divided into five segments and each was scored as follows: 1, normal contraction; 2, mild hypokinesia; 3, severe hypokinesia, 4, akinesia; 5, dyskinesia; 6, aneurysm formation.

The sum of all the segments' scores gives a total left ventricular score. A normal result is 10 and higher scores indicate greater degrees of left ventricular dysfunction. In addition to this numerical scoring system we examined each left ventricular angiogram for an aneurysm, defined as discrete regional systolic expansion.

We used χ^2 analysis to compare the angiographic variables of the two study groups.

Results

CHARACTERISTICS OF GROUPS (TABLE)

The table shows the differences between the patients with septal rupture and the comparison post-infarction group. Patients with septal rupture were older (63 yr *v* 54 yr), had a more even ratio of men to women (2:1), and a greater preponderance of anterior infarctions (70% *v* 40%). The two groups overall had a similar interval from infarction to angiography, but some patients with septal rupture presented a considerable time after infarction. The longest interval was more than a year. Most patients with septal rupture were investigated within two weeks of infarction and within a few days of the diagnosis of septal rupture (median interval 12 days (range 1–470). The median delay in the comparison group was 21 days (range 7–40) from infarct to angiography.

CORONARY ANGIOGRAPHY (TABLE, FIGS 1 AND 2)

Anterior infarction was more common in patients with septal rupture and this accorded with the higher rate of occlusion of the left anterior descending artery (70%). Total occlusion of the infarct vessel was more common in those with septal rupture than in the

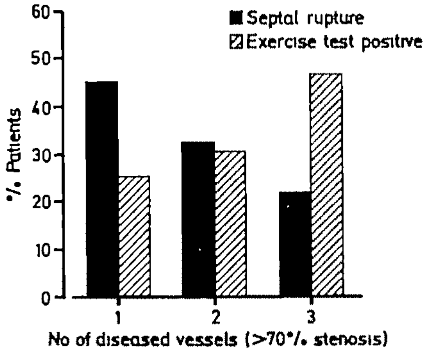


Fig 2 *Extent of coronary disease at angiography in patients with septal rupture after myocardial infarction and in a comparison group with a positive submaximal exercise test after myocardial infarction.*

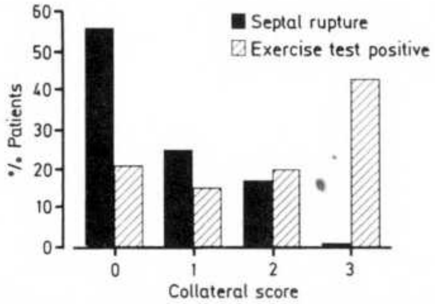


Fig 3 *Extent of collateral circulation to the infarct related artery in patients with septal rupture after infarction and in a comparison group with a positive submaximal exercise test after infarction.*

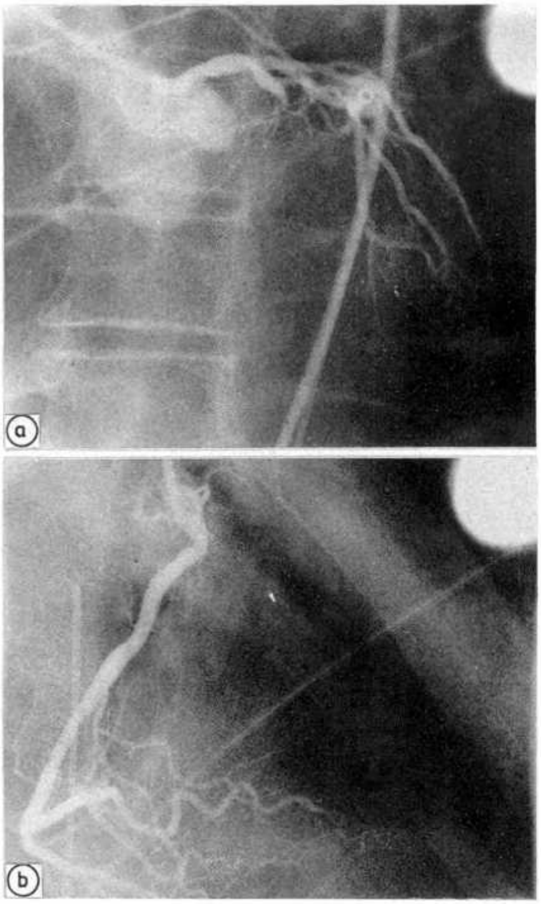


Fig 4 *Coronary angiography in a patient after anterior infarction complicated by septal rupture. The left coronary angiogram (a) shows occlusion of the anterior descending branch which has no collateral filling of the distal vessel from the right coronary artery (b).*

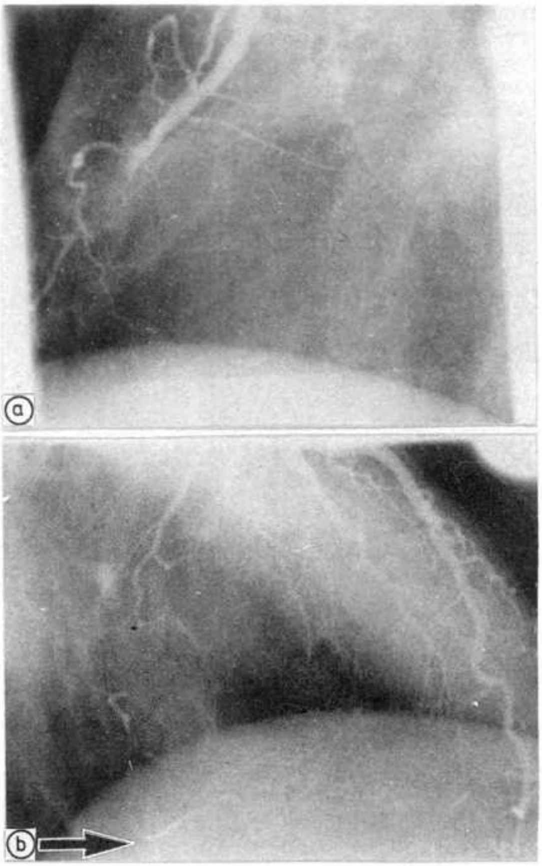


Fig 5 *Coronary angiography in a stable patient soon after inferior infarction. The right coronary angiogram (a) is occluded. The left coronary angiogram (b) shows good distal filling of the right coronary artery via collaterals.*

comparison group (92% *v* 79%, $p < 0{\cdot}01$). There was more single vessel disease than triple vessel disease in those with septal rupture (43% *v* 24%). The reverse was true in the comparison group ($p < 0{\cdot}01$) (25% single vessel disease and 45% triple vessel disease).

COLLATERAL CIRCULATION TO INFARCT RELATED ARTERY (FIGS 3, 4, AND 5)

We found a striking and highly significant difference ($p < 0{\cdot}001$) in the pattern of collateral circulation to the infarct territory in the two study groups. Over half (56%) of the patients with septal rupture had no angiographically demonstrable collaterals and a further 26% had only faint (grade 1) branch vessel filling. Just one of the 91 patients had a grade 3 collateral supply to the epicardial portion of the infarct related artery. In the comparison group, however, over half had well developed collateral circulation with grade 3 (45%) or 2 (20%) scores. Ranking the patients (either group) according to the interval since infarction, age, or site of infarction or degree of left ventricular impairment made no difference to the results of collateral scoring.

LEFT VENTRICULAR ANGIOGRAPHY (TABLE)
Another clear and statistically significant difference between the study groups was the frequency of aneurysm formation. There was a left ventricular aneurysm in 66% of the septal rupture group and only 24% of the comparison group ($p < 0.0001$) and patients with septal rupture showed a greater degree of left ventricular damage as judged by the regional wall motion score. They had a higher mean score than the comparison group (28 *v* 22 $p < 0.01$).

Discussion

This series of 91 patients with post-infarction ventricular septal defect from two referral centres gives a broad clinical experience of this condition. In the past clinical attitudes favoured delayed transfer to referral centres such as our hospitals, and this probably would have led to many of these high risk patients dying before investigation and operation.[2]

In patients with septal rupture there were fewer collaterals to the infarct territory. Our comparison group, chosen because of the short interval from infarction to angiography, had more three vessel disease than those with septal rupture. An earlier report on early angiography in a large unselected consecutive group of survivors of infarction showed a similar pattern of coronary disease to that seen in our patients with ventricular septal defects.[7] But 61% had collaterals—a similar proportion to that found in our comparison group. This emphasises the lack of collateral circulation associated with ventricular septal rupture.

Human collateral circulation varies[8] and its pattern of development is unclear. Coronary collateral vessels are thought to enlarge in the presence of obstructive coronary disease creating a pressure gradient and encouraging flow between the epicardial coronary arteries.[9] In acute coronary occlusion, collateral circulation may be seen immediately but its functional importance and time course of development are not known in humans. Reports from a series of patients studied after infarction, who had occlusion of the infarct vessel, give some insight to the rate of progression of collaterals.[10] Just 16% had collaterals visible on angiography within six hours but after the first day the rate rose to 62% (grade II–III collateral score) with only small increases in the following weeks. This suggests that the small differences in the intervals from infarction to angiography in our two groups are unlikely to have influenced the results significantly. Sporadic case reports have indicated that a collateral circulation may be well developed in the absence of chronic obstructive disease and protect the heart after ligation of the left anterior descending artery[11] or traumatic right coronary arteriocameral fistula.[12] Large retrospective studies of patients with coronary disease have given an indication of the functional importance of collaterals seen on coronary angiography. Evidence from studies of regional wall motion supports the view that collaterals protect the heart when coronary occlusion occurs.[13 14] This effect was of more benefit after occlusion of the left anterior descending artery than after occlusion of the right coronary artery.[15]

Our findings indicate that septal rupture after infarction is most likely to be associated with total occlusion of a coronary artery (usually the left anterior descending artery) with little or no collateral flow to the infarct territory. The absence of collateral flow probably increases regional necrosis leading to an increased risk of left ventricular aneurysmal dilatation and septal rupture. Alternatively, the absence of collateral circulation could simply reflect the extensive myocardial damage. This is unlikely in view of the equal distribution of collaterals in our comparison group irrespective of the extent of left ventricular damage. If our original hypothesis were correct then the pattern of coronary artery disease in patients with rupture of the left ventricular free wall should be similar—data from necropsy studies support this view.[16] In 20 cases postmortem angiography showed a recent occlusion in a coronary artery with no collateral circulation to the infarct territory.

Doppler echocardiography is a reliable method for the diagnosis of ventricular septal rupture after myocardial infarction and it has been suggested that invasive investigation before operation might be unnecessary.[17 18] Our results show that single vessel disease was more common in patients with septal rupture than in the comparison group. But half of the septal rupture group did have disease in the non-infarct related vessels (30% two vessel disease, 21% three vessel disease) of sufficient severity to be considered for aortocoronary bypass grafting. Establishing the diagnosis of septal rupture should not now require cardiac catheterisation, but coronary angiography remains a useful preoperative investigation.

This review of patients with septal rupture confirmed our initial clinical impression that most cases occurred in elderly patients with single vessel disease, total occlusion of the infarct vessel, and no collateral support to a large area of infarction. The angiographic appearance was different from that seen in a stable group of patients who were also assessed soon after infarction.

References

1 Fox AC, Glassman E, Isom OW. Surgically remedial complications of myocardial infarction. *Prog Cardiovasc Dis* 1979;**21**:461–84.

2 Norell MS, Gershlick AH, Pillai R, *et al.* Ventricular septal rupture complicating myocardial infarction: is earlier surgery justified? *Eur Heart J* 1987;**8**:1281–6.

3 Loisance DY, Cachera JP, Poulain H, Aubry PH, Juvin AM, Galey JJ. Ventricular septal defect after acute myocardial infarction. Early repair. *J Thorac Cardiovasc Surg* 1980;**80**:61–7.

4 Scanlon PJ, Montoya A, Johnson SA, *et al.* Urgent surgery for ventricular septal rupture complicating acute myocardial infarction. *Circulation* 1985;**72** (suppl II):185–90.

5 de Belder MA, Pumphrey CW, Skehan JD, *et al.* Relative power of clinical, exercise test, and angiographic variables in predicting clinical outcome after myocardial infarction: the Newham and Tower Hamlets study. *Br Heart J* 1988;**60**:377–89.

6 The National Heart, Lung and Blood Institute Coronary Artery Surgery Study (CASS). The principal investigators of CASS and their associates. *Circulation* 1981;**63**(suppl I):1–65.

7 Bosch X, Theroux P, Waters DD, Pellitier GB, Roy D. Early postinfarction ischaemia: clinical, angiographic and prognostic significance. *Circulation* 1987;**75**: 988–95.

8 Fulton WFM. *The coronary arteries.* Springfield, Illinois: Charles C Thomas, 1965:127–8.

9 Blumgart HL, Schlesinger MJ, Zoll PM. Angina pectoris, coronary failure and acute myocardial infarction. The role of coronary occlusions and collateral circulation. *JAMA* 1941;**116**:91–7.

10 Lieboff RH, Schwartz H. Clinical sequelae: special patient subsets, incomplete occlusion of the infarct-related artery and coronary collaterals. *Circulation* 1987;**76**(suppl II):115–20.

11 Carleton RA, Boyd T. Traumatic laceration of the left anterior descending artery treated by ligation without myocardial infarction. Report of a case with review of the literature. *Am Heart J* 1958;**56**:136–42.

12 Siepser SL, Kaltman AJ, Mills N, Pughkem T, Fox AC. Coronary collateral flow after traumatic fistula between right coronary artery and right atrium. *N Engl J Med* 1972;**287**:754–6.

13 Carroll RJ, Verani MS, Falsetti HL. The effect of collateral circulation on segmental left ventricular contraction. *Circulation* 1974;**50**:709–13.

14 Kolibash AJ, Bush CA, Wepsic RA, Schroeder DP, Tetalman MR, Lewis RP. Coronary collateral vessels: spectrum of physiologic capabilities with respect to providing rest and stress myocardial perfusion, maintenance of left ventricular function and protection against infarction. *Am J Cardiol* 1982;**50**:230–8.

15 Hamby RI, Aintablian A, Schwartz A. Reappraisal of the functional significance of the coronary collateral circulation. *Am J Cardiol* 1976;**38**:305–9.

16 Wessler S, Zoll PM, Schlesinger MJ. The pathogenesis of spontaneous cardiac rupture. *Circulation* 1952;**6**: 334–51.

17 Cheeseman MG, John R, Murray N, Redding VJ. Pulsed Doppler ultrasound in the diagnosis of post-infarction ventricular septal defect [Abstract]. *Br Heart J* 1987;**57**:563.

18 MacLeod D, Fananapazir L, de Bono D, Bloomfield P. Ventricular septal defect after myocardial infarction: assessment by cross sectional echocardiography with pulsed wave Doppler scanning. *Br Heart J* 1987;**58**: 214–7.

Br Heart J 1989;**62**:273–80

Cigarette smoking and non-fatal myocardial infarction in women: is the relation independent of coronary artery disease?

DAVID S FREEDMAN,*¶ HARVEY W GRUCHOW,* JOHN A WALKER,† STEVEN J JACOBSEN,* ALFRED J ANDERSON,‡ KATHLEEN A SOBOCINSKI,* JOSEPH J BARBORIAK§||

*From the *Division of Biostatistics and Clinical Epidemiology, and §Department of Pharmacology and Toxicology, Medical College of Wisconsin; and †Cardiology Section, and ‡Cardiovascular Disease Data Registry, St Luke's Hospital; and ||Milwaukee Veterans Administration Medical Center, Milwaukee, Wisconsin, USA*

SUMMARY The relation of cigarette smoking to both coronary disease and non-fatal myocardial infarction was examined in a cross sectional study of 1053 women who underwent coronary arteriography. As compared with the 489 women who had never smoked cigarettes, ever-smokers (mean duration of smoking, 25 years) were 1·6 times as likely to have significant stenotic disease and were 1·9 times as likely to have suffered a myocardial infarction. These associations were strongest in women under 50 years of age, with odds ratios of 3·5 for coronary artery disease and 4·5 for myocardial infarction. Although the extent of stenotic disease and prior myocardial infarction were strongly associated, women who smoked cigarettes remained at increased risk of a myocardial infarction even after their increased coronary artery disease had been taken into account. For example, heavy smokers (>30 pack-years) were 2·3 times as likely to have had a myocardial infarction as were non-smokers; controlling for the extent of stenotic disease (in addition to age and other risk factors) reduced the estimated relative risk to only 1·9. Stratified analyses showed that this increased risk for clinical disease among smokers was evident at all levels of occlusion, even among women with minimal stenotic disease. These results, collected at the time of arteriography, suggest that non-atherogenic mechanisms may be important in the aetiology of myocardial infarction among women who smoke cigarettes.

Cigarette smoking is widely recognised as an important risk factor for coronary heart disease in men, with the risk of myocardial infarction and sudden death increasing with the number of cigarettes smoked daily.[1,2] Recent case-control[3,4] and cohort[5-7] studies have also reported an increased risk of coronary heart disease among female smokers. In general, women who smoke cigarettes are two to four times as likely to develop clinical disease as are non-smokers, with younger women and those smoking more than one pack daily showing the greatest increase in risk.[3,4,7]

It is uncertain, however, whether the excess coronary heart disease among smokers is caused by more extensive coronary atherosclerosis. Although cigarette smokers have an atherogenic lipoprotein profile, their increased mortality from cardiovascular disease is independent of lipid concentrations.[8] In addition, smokers do not consistently show increased coronary atherosclerosis upon pathological examination,[9] and there is a high prevalence of cigarette smoking among patients who have clinical evidence of a myocardial infarction but unobstructed coronary arteries.[10,11] Therefore, non-atherogenic mechanisms, such as nicotine and carboxyhaemoglobin,[12] fibrinogen,[13,14] or white blood cells,[15] may be involved in the aetiology of cardiovascular disease among smokers.

Requests for reprints to Dr Joseph J Barboriak, Milwaukee Veterans Administration Medical Center, Milwaukee, WI 53295, USA.

¶Present address: Centers for Disease Control, F-16, 1600 Clifton Road, Atlanta, GA 30333, USA.

Accepted for publication 14 June 1989

CALCUTTA
CENTRAL
LIBRARY

Because it gives information on both coronary artery disease and previous non-fatal myocardial infarction, coronary arteriography provides a unique opportunity to assess the importance of occlusive disease and non-atherogenic factors in the development of coronary heart disease.[16] For example, we have shown that even after controlling for the extent of coronary occlusion, "heavy" cigarette smoking doubles the risk for non-fatal myocardial infarction among men,[17] suggesting that smoking may be involved in the precipitation of a myocardial infarction rather than in the development of atherosclerosis. Previous arteriography studies examining the relation of cigarette smoking to coronary artery disease have yielded conflicting results, ranging from a strong, positive association[18] to a non-significant, negative relation.[19]

Because smoking may account for over a half of all coronary heart disease in women below the age of 55,[3,7] it is important to elucidate the possible mechanism(s) of this association. Therefore, the current study uses data collected at the time of arteriography to examine the relation of cigarette smoking to non-fatal myocardial infarction. The object was to determine whether the increased risk of myocardial infarction among female cigarette smokers is attributable to increased stenotic disease.

Patients and methods

POPULATION AND DISEASE STATE

The Milwaukee Cardiovascular Data Registry consists of patients referred to two Milwaukee hospitals (St Luke's and the Milwaukee Veterans Administration Center) for diagnostic coronary arteriography. Although selection of patients for coronary arteriography varies,[20] criteria include (*a*) unstable angina pectoris, (*b*) moderate to severe stable angina, (*c*) recurrent chest pain of unknown origin, and (*d*) previous myocardial infarction or coronary artery bypass surgery. The present analyses are restricted to a subset of the 1627 white women who underwent arteriography between 1972 and 1986, and for whom concentrations of total cholesterol and triglycerides were measured. Other races represented $<5\%$ (n = 95) of all female patients and were therefore excluded.

The extent of obstructive disease was evaluated, without knowledge of risk factor data, by a radiologist and cardiologist experienced in the interpretation of arteriograms. Although the reproducibility of these readings was not assessed, the degree of observer variability[21] and disagreement with postmortem pathology findings[22] is known to be moderate.

Reductions in lumen diameter caused by the most severe stenosis in the left main, left anterior descending, circumflex, and right coronary arteries were estimated, and results were incorporated into an occlusion score reflecting the overall severity of coronary artery disease. As previously reported[17,23] a scale suggested by Rowe *et al*[24] was inverted, with 0 representing "no observed narrowing of any artery," and a score of 300 indicating "total occlusion of the major vessels." (The mean occlusion score was 77.) The number of diseased vessels was also recorded: a $\geqslant 75\%$ narrowing of the left anterior descending, circumflex, and right coronary arteries was regarded as clinically important.

INFORMATION ON RISK FACTORS

Medical records and questionnaires were used to obtain data before arteriography on smoking history, weight, height, alcohol consumption, medication use; and histories of hypertension, angina, diabetes mellitus, and previous myocardial infarction. Women were excluded from the analyses if they reported use of thyroid or cholesterol-lowering medication, oral contraceptives, sex hormones, or had hypothyroidism or hyperthyroidism. These restrictions eliminated 558 patients, with use of sex hormones accounting for the largest category (n = 265) of exclusions. For the remaining 1069 (1627 − 558) women, reported intake of beer, wine, and mixed drinks was converted to ml of absolute alcohol per week. The body mass index (kg/m^2) was used as an estimate of obesity for each woman.

After an overnight fast, blood samples were collected before arteriography. Plasma concentrations of total cholesterol and triglycerides were measured by automated procedures[25-27] in a laboratory that has been standardised (and is monitored) by the Centers for Disease Control. Concentrations of high density lipoprotein cholesterol were first measured in 1977; 261 women had recorded concentrations of this lipoprotein fraction.

CIGARETTE SMOKING

The cigarette smoking category (current/past/never) of 1053 women could be determined through questionnaire. Past (n = 374) and current (n = 190) smokers showed similar levels of (*a*) most risk factors, (*b*) coronary artery disease, and (*c*) the prevalence of prior myocardial infarction. Because many of the ex-smokers were likely to have stopped smoking after a myocardial infarction (the year of stopping was not known), most analyses contrasted ever-smokers with never-smokers. (Certain analyses, however, separated the ever-smokers into past and current smokers.) Data on the duration (years) of cigarette smoking and the approximate number of cigarettes smoked daily (<5, 10, 20, 30, or >40) were available for 521 of the 564 women who reported that they had ever smoked. These data were used to calculate pack-years by multiplying the usual number of packs smoked daily by the number of years of smoking. Of women who reported that they had ever smoked, the median duration of smoking was 26 years; 84% had smoked for > 10 years.

HISTORY OF NON-FATAL MYOCARDIAL INFARCTION

A history of myocardial infarction for each patient was also obtained through a questionnaire administered before catheterisation. The specific question was, "Has your doctor ever said that you have had a heart attack?"; 334 (32%) women reported that they had suffered a heart attack.

The accuracy of these responses was not validated for these women, and false positive and false negative responses were probably reported.[28 29] None the less, a previous study from the Milwaukee Cardiovascular Data Registry found that 93% of self-reported myocardial infarctions among 465 men who underwent a coronary bypass operation were confirmed by data in their medical records.[17]

STATISTICAL ANALYSES

Mean values of cigarette smoking and other risk factors were first contrasted according to the myocardial infarction state and the number of diseased vessels (0 *v* ≥1). The relation of cigarette smoking to both stenotic disease and myocardial infarction was then assessed in three age groups (<50, 50–59, and ≥60 years), and odds ratios were calculated as estimates of relative risk. The relative importance of smoking duration versus daily consumption in the relation of smoking to myocardial infarction was evaluated by logistic regression with indicator variables representing three levels of each exposure variable.

We then examined the independent relation of cigarette smoking to myocardial infarction by controlling for the extent of coronary artery disease. The occlusion score was categorised into five groups, and the association between smoking and myocardial infarction was examined within each stratum. Results were summarised over the strata using Mantel-Haenszel odds ratios, and the Mantel extension was used to test for a trend.[30]

The relation of pack-years (number of packs smoked per day × duration of smoking) to myocardial infarction was then assessed by logistic regression. Predictor variables in the various models included: (*a*) pack-years only; (*b*) pack-years and the occlusion score; and (*c*) pack-years, occlusion, and other risk factors. (The extent of coronary artery disease was treated as a risk factor for myocardial infarction in these last two models.) To avoid assumptions about the shape of the association between pack-years and myocardial infarction,[31] dummy variables (representing categories of pack-years) were used in these analyses.[32] Logistic regression models were also used to assess possible differences in the relation of cigarette smoking to myocardial infarction between past and current smokers.

Results

Mean values of several characteristics were first examined according to reported smoking state (never/past/current) before arteriography (data not shown). Despite a higher prevalence of hypertension among women who had never smoked, non-fatal myocardial infarctions were more common among both ex-smokers and current smokers, with estimated relative risks of 2·1 and 1·6, respectively. In addition, mean occlusion scores were approximately 25 points higher among both ex-smokers and current smokers than among women who had never smoked. Current (but not past) smokers also had slightly lower values of body mass index than did women who had never smoked (25·1 *v* 26·2 kg/m^2) and both current and past smokers had raised concentrations of triglycerides (1·81 and 1·90 *v* 1·67 mmol/l) (161 and 168 *v* 148 mg/dl) and alcohol intake (69 and 118 *v* 44 ml/week). Because past and current smokers showed similar (*a*) risk factor values, (*b*) amounts of coronary artery disease, and (*c*) risk of previous myocardial infarction, most analyses contrasted ever-smokers (n = 564) with never-smokers (n = 489).

We then examined differences in risk factor values according to non-fatal myocardial infarction and clinically important occlusive disease (table 1). The two variables were strongly related: the mean occlusion score was approximately twice as large (117 *v* 58) among women who reported a myocardial infarction as in other patients. In general, however, risk factors were more strongly related to coronary artery disease. For example, concentrations of total cholesterol were 0·7 mmol/l (27 mg/dl) higher in women with occlusive disease than in those with no diseased vessels, but the difference between those with and those without a history of myocardial infarction was only 0·2 mmol/l (6 mg/dl). Smoking state (ever *v* never), triglyceride concentrations, hypertension, and diabetes were the only characteristics significantly related to both coronary artery disease and myocardial infarction.

Women who had smoked cigarettes had a higher mean occlusion score than non-smokers (91 for ex-smokers, 79 for current smokers, 65 for never-smokers) and were 1·6 (current) to 2·1 (past) times as

Table 1 *Mean (SD) values of selected variables in women according to previous myocardial infarction and coronary artery disease*

	Previous myocardial infarction				*Number of diseased vessels†*			
	No (n = 719)		*Yes (n = 334)*		*0 (n = 634)*		*≥1 (n = 419)*	
Occlusion score	58	(80)**	117	(87)**	17	(35)**	169	(57)**
Age (years)	56	(10)	57	(9)	55	(11)**	58	(9)**
Ever-smoked (%)	49**		64**		49**		61**	
% smoking ≥30 years‡	44		49		38**		54**	
% smoking > 1 pack per day‡	24		28		22		30	
Total cholesterol (mmol/l)	6·0	(1·3)	6·2	(1·3)	5·8	(1·2)**	6·5	(1·3)**
Triglycerides (mmol/l)	1·7	(1·1)**	2·0	(1·1)**	1·6	(0·9)**	2·1	(1·3)**
HDL cholesterol (mmol/l)§	1·2	(0·4)	1·1	(0·3)	1·3	(0·4)**	1·0	(0·3)**
Body mass index (kg/m^2)	26·0	(5·2)	26·1	(4·8)	25·9	(5·5)	26·3	(4·4)
Alcohol intake (ml/wk)	68	(139)	54	(90)	67	(125)	59	(128)
History of:								
Angina (%)	60		67		56**		73**	
Hypertension (%)	46*		55*		44**		57**	
Diabetes (%)	7**		13**		6**		13**	

HDL, high density lipoprotein.

p values compare mean concentration (or proportions) in categories of previous myocardial infarction or number of diseased vessels: *$p < 0·01$; **$p < 0·001$.

†Based on ≥75% narrowing of any vessel.

‡Restricted to women who had ever smoked.

§Restricted to women with recorded concentrationns of HDL cholesterol: 187 without a myocardial infarction, 74 with a myocardial infarction, 154 without coronary artery disease, and 107 with coronary artery disease.

likely to have suffered a myocardial infarction. These increased risks, however, varied with age (table 2). Among women under 50 years of age, smoking was strongly related to both coronary artery disease (odds ratios of 3·6 (past) and 3·3 (current)) and non-fatal myocardial infarction (odds ratios of 5·0 and 4·1). In contrast, all estimated risks were ≤2 among women who were ≥50.

Table 3 shows the relation of cigarette smoking to myocardial infarction after controlling for the extent of coronary artery disease by stratification. Although many of the cells contain small numbers, 13 of the 15 odds ratios for daily cigarette consumption were > 1 and 11 of the odds ratios for smoking duration were > 1. Even among women with minimal stenotic disease (occlusion score <50), the risk of myocardial infarction was increased almost twofold among women who smoked > 1 pack daily. Mantel-Haenszel summary odds ratios showed that after controlling for occlusive disease, cigarette smoking remained significantly associated with myocardial infarction. Furthermore, most adjusted odds ratios were very similar to estimates that did not take the extent of coronary artery disease into account.

Table 2 *Relation of cigarette smoking to coronary artery occlusion and non-fatal myocardial infarction*

			Number of diseased vessels†					*Myocardial infarction*		
Age group (yr)	*Smoking state*	*(No)*	*0*	*1*	*2*	*3*	*Odds ratio‡*	*No*	*Yes*	*Odds ratio*
<50	Never	(97)	82	9	3	3		85	12	
	Past	(75)	45	16	10	4	3·6***	44	31	5·0***
	Current	(79)	49	20	7	3	3·3***	50	29	4·1***
50–59	Never	(176)	127	30	12	7		131	45	
	Past	(165)	94	37	23	11	2·0**	107	58	1·6
	Current	(63)	39	15	6	3	1·6	47	16	1·0
≥60	Never	(216)	116	49	28	23		153	63	
	Past	(134)	57	37	28	12	1·6*	73	61	1·9**
	Ever	(48)	25	8	10	5	1·1	29	19	1·6
Overall	Never	(489)	325	88	43	33		369	120	
	Past	(374)	196	90	61	27	1·8***	224	150	2·1***
	Current	(190)	113	43	23	11	1·4	126	64	1·6*

*$p < 0·05$; **$p < 0·01$; ***$p < 0·001$.

†75% narrowing of the left anterior descending, circumflex, or right coronary arteries.

‡Contrasting 0 vessel disease with ≥1 vessel disease; the reference categories (odds ratio = 1) are never-smokers.

Table 3 *Relation of cigarette smoking in women† to non-fatal myocardial infarction (stratified by the occlusion score)*

	Coronary artery occlusion category											
	0–49		*50–99*		*100–149*		*150–199*		*≥200*		*Summary ORs*	
Myocardial farction:	*No*	*Yes (OR)*	*No*	*Yes (OR)*	*No*	*Yes (OR)*	*No*	*Yes (OR)*	*No*	*Yes (OR)*	*Unadjusted*	*Adjusted‡*
Non-smokers	241	43	42	18	35	11	23	20	28	28		
Packs/day.												
<1	72	14 (1·1)	14	13 (2·2)	11	16 (4·6)**	8	10 (1·4)	14	14 (1·0)	1·7**	1·6*
1	81	18 (1·2)	6	9 (3·5)*	10	13 (4·1)**	13	13 (1·1)	15	19 (1·3)	1·8**	1·6*
>1	35	12 (1·9)	14	9 (1·5)	12	14 (3·7)*	8	14 (2·0)	11	9 (0·8)	2·2**	1·8**
Duration (years).												
1–20	47	19 (1·4)	14	6 (1·0)	4	4 (3·2)	6	5 (1·0)	6	12 (2·0)	1·4	1·5
20–29	50	8 (0·9)	4	10 (5·8)**	11	12 (3·5)*	8	14 (2·0)	6	10 (1·7)	2·1**	1·9**
≥30	64	17 (1·5)	16	15 (2·2)	18	27 (4·8)**	15	18 (1·4)	28	20 (0·7)	2·1**	1·6**

OR, odds ratio.
Stratum-specific p values were computed by Fisher's exact test. The overall association was tested by the summary odds ratio.
p < 0·05; **p < 0·01
Restricted to 489 never-smokers and 521 smokers who reported both frequency and duration of smoking.
Mantel-Haenszel summary odds ratio.

However, the association between smoking and myocardial infarction decreased from 2·1 to 1·6 among women who had smoked for more than 30 years.

We assessed the relative importance of smoking duration and daily consumption of cigarettes among ever-smokers (table 4). Among these women, the estimated risk of myocardial infarction tended to be more strongly related to daily consumption (with odds ratios increasing from 1·6 to 2·4) than to duration (1·1 to 1·5). Because a small independent effect of duration on myocardial infarction risk was seen, however, daily consumption and duration were combined to form pack-years in subsequent analyses.

Table 5 shows the relation of pack-years to myocardial infarction in three logistic regression models. Model 1, which contains only indicator variables that represent the three categories of pack-years, shows that the estimated risk of myocardial infarction among smokers increased from 1·5 to 2·3 with increasing number of pack-years. Furthermore, with the exception of women who had been smoking for ≥30 pack-years, these associations were unaffected by controlling for the extent of stenotic disease (model 2). (Including the extent of stenotic disease as an independent variable, however, greatly improved the prediction of myocardial infarction.) Furthermore, the effect of cigarette smoking was also independent of other risk factors (model 3). The joint contribution of eight additional risk factors in predicting myocardial infarction was only marginally significant ($p = 0·11$).

Table 4 *Cross classification of risk of myocardial infarction in women by duration and amount of smoking**

Smoking duration (yr)	*Number of packs smoked daily*			*Adjusted† odds ratio*
	<1	*1*	*>1*	
1–19	1·3‡ (80)	1·6 (46)	2·5 (24)	1·1
20–29	2·1 (43)	1·8 (53)	4·5 (37)	1·7
≥30	2·4 (63)	2·0 (98)	2·6 (77)	1·5
Adjusted odds ratio†	1·6	1·5	2·4	

*Restricted to women who had ever smoked.
†Adjusted levels for each duration or frequency category
‡Estimated risk of myocardial infarction relative to non-smokers. Values have been adjusted by logistic regression for age, total cholesterol, triglycerides, alcohol intake, body mass index, and histories of hypertension and diabetes. Sample size for duration-amount category is shown in parentheses

Additional regression models that included indicator variables representing (*a*) past *v* never smokers, and (*b*) current *v* never smokers, were then constructed to assess possible differences among ever-smokers (data not shown). Results indicated that controlling for the extent of coronary artery occlusion reduced the unadjusted odds ratios from 2·1 to 1·9 among ex-smokers and did not alter the odds ratio of 1·6 among current smokers.

Discussion

The relative risk of cardiovascular disease among cigarette smokers compared with non-smokers varies according to the clinical entity examined: relative risks range from 1 for angina pectoris to >10 for sudden death.[6] In addition, the excess risk of myocardial infarction among cigarette smokers drops by 50% within the first year after stopping smoking,[33] and despite high rates of clinical disease, cigarette smokers have not consistently been found to have increased amounts of coronary atherosclerosis.[34] Therefore, smoking may be an acute precipitant for

Table 5 *Multivariable relation* of pack-years to non-fatal myocardial infarction in women*

	Model					
	1		*2*		*3*	
Predictor variable	*OR*	*(95% CI)*	*OR*	*(95% CI)*	*OR*	*(95% CI)*
Pack-years†:						
<15	1·5	(1·0, 2·3)	1·5	(1·0, 2·4)	1·6	(1·0, 2·5)
15–29	1·7	(1·1, 2·7)	1·7	(1·1, 2·7)	1·8	(1·1, 2·8)
≥30	2·3	(1·6, 3·4)	1·9	(1·3, 2·8)	1·9	(1·3, 2·9)
Occlusion score‡			1·8	(1·6, 2·1)	1·8	(1·5, 2·1)
Other risk factors§					—	—
Degrees of freedom	3		4		12	
2 × Maximised log likelihood	−1036		−971		−958	

OR, odds ratio; CI, confidence interval.

*Estimated by logistic regression Restricted to women with recorded levels of all covariates (n = 860).

†The effect of each smoking category is estimated relative to non-smokers.

‡Standardised odds ratio associated with a 1 standard deviation change in the predictor variable.

§Age, age^2, total cholesterol, triglycerides, body mass index, alcohol intake, and histories of hypertension and diabetes

coronary heart disease, possibly related to the development of a thrombus over an ulcerated plaque, rather than an influence on the progression of the atherosclerotic lesion. Previous case reports suggest that cigarette smoking can precipitate a myocardial infarction even among persons with minimal stenotic disease.[10 11]

The results of the current study, which closely accord with earlier findings of Hartz *et al* in men,[17] document the importance of these non-atherogenic effects in women. Overall, female patients who had ever smoked cigarettes were 1·9 times as likely to have suffered a myocardial infarction as were those who had never smoked. Although cigarette smokers also had significantly more stenotic disease than did non-smokers, this accounted for little of their increased risk for myocardial infarction; controlling for the extent of occlusive disease yielded an odds ratio (ever-smokers *versus* never-smokers) of 1·7. Controlling for coronary artery disease, however, did reduce the risk of myocardial infarction among women who had smoked for more than 30 years (unadjusted odds ratio = 2·1 *v* 1·6, adjusted). These results suggest that while the non-atherogenic effects of smoking may predominate, smoking-related increases in coronary atherosclerosis are also important in the aetiology of myocardial infarction among long term smokers.

Although female patients undergoing arteriography are not representative of all women with coronary artery disease, several of the current results accord closely with those from less selected populations. Increased concentrations of triglycerides were seen among patients who reported smoking cigarettes. In addition, as reported by others, the relation of smoking to myocardial infarction was strongest in relatively young women,[3 4 6] and increased with the amount smoked daily.[1 2 7] Results from the Lipid Research Clinics Follow-up Study also show that the effects of cigarette smoking on cardiovascular disease are not attributable to adverse lipid concentrations,[8] and population-based studies have failed to show consistently increased coronary atherosclerosis among cigarette smokers.[9] Therefore, non-atherogenic mechanisms may be important in the precipitation of coronary heart disease not only among persons undergoing coronary arteriography, but also in the general population. Coronary arteriography, however, provides a unique opportunity to control for the extent of coronary atherosclerosis in assessing the stage of disease at which risk factors act.

In addition to the non-representativeness of women in the current study, however, other methodological questions should be considered in interpreting these results. Because it is cross-sectional, risk factor values may not accurately reflect values in the past, and it is possible that many of the ex-smokers stopped smoking shortly before arteriography, perhaps after a myocardial infarction. (This possibility is supported by the slightly higher risk associated with past, as opposed to current, smoking state.) To minimise this misclassification, however, past and current smokers were combined in most analyses in the current study; 90% of these ever-smokers had smoked for >7 years. In addition, the current analyses studied survivors of a myocardial infarction, and it is possible that the effects of cigarette smoking on sudden death may differ from those seen for *non-fatal* myocardial infarction.

Inaccurate responses were also probably recorded for previous myocardial infarction. Although population surveys indicate that false positive responses in men may exceed 20%,[28,29] women who underwent coronary arteriography in the current study were likely to have been more familiar with their medical diagnoses. For example, as previously observed in the Milwaukee Cardiovascular Data Registry, only 7% of self-reported heart attacks among 465 men could not be confirmed by data in their medical records.[17] Furthermore, women who reported a myocardial infarction in the current study had higher triglyceride concentrations and more extensive stenotic disease than did other women; occlusion scores were 117 and 58, respectively. Because smokers are (*a*) less likely to survive an initial myocardial infarction,[35,36] and (*b*) patients who had suffered a myocardial infarction might under-report their smoking habits, the importance of cigarette smoking may have been underestimated in this study.

A myocardial infarction is typically caused by a thrombosis superimposed on a stenosed vessel, and therefore, risk ractors for coronary heart disease may act either by increasing the extent of coronary artherosclerosis or by precipitating the terminal event. There are numerous mechanisms whereby smoking could influence the risk of myocardial infarction independently of occlusive disease,[34] and even without increased coronary artery disease, the frequency and duration of ischaemic episodes seem to be greatly increased among smokers.[37] Cigarette smokers have raised white blood cell counts, and much evidence indicates that this is a strong predictor of myocardial infarction, possibly because raised counts can obstruct small vessels or injure endothelial cells.[15] Smoking also affects haemostatic and clotting factors,[38] and the relation of smoking to subsequent myocardial infarction is partly mediated by increased concentrations of fibrinogen among smokers.[14] Other mechanisms, including the toxic effects of carbon monoxide and nicotine[12] or alterations in vessel diameter[39] may be involved in the pathogenesis of myocardial infarction among cigarette smokers.

Although the specific mechanisms have not been documented, the current findings show the importance of the non-atherogenic effects of cigarette smoking in the development of myocardial infarction among women. Irrespective of the extent of coronary artery disease, cigarette smokers are at increased risk for a myocardial infarction, and other findings suggest that they could quickly reduce their excess risk by stopping smoking.[33] Unfortunately, the smokers at highest risk are not stopping their habit at the same rate as are those at less risk.[40] Even among women who undergo arteriography, a large proportion continue to smoke.

We acknowledge the interest and support of members of the Milwaukee Cardiovascular Data Registry.

Supported by grants from the National Institute of Health and by the Medical Research Service of the Veterans Administration.

References

1 The Pooling Project Research Group. Relationship of blood pressure, serum cholesterol, smoking habit, relative weight and ECG abnormalities to incidence of major coronary events: final report of the Pooling Project. *J Chronic Dis* 1978;31:201–306.

2 Neaton JD, Kuller LH, Wentworth D, Borhani NO. Total and cardiovascular mortality in relation to cigarette smoking, serum cholesterol concentration, and diastolic blood pressure among black and white males followed up for five years. *Am Heart J* 1984; 108:759–69.

3 Slone D, Shapiro S, Rosenberg L, *et al.* Relation of cigarette smoking to myocardial infarction in young women. *N Engl J Med* 1978;298:1273–6.

4 Rosenberg L, Shapiro S, Kaufman DW, Slone D, Miettinen O, Stolley PD. Cigarette smoking in relation to the risk of myocardial infarction in young women. Modifying influence of age and predisposing factors. *Int J Epidemiol* 1980;9:57–63.

5 Doll R, Gray R, Hafner B, Peto R. Mortality in relation to smoking: 22 years' observations on female British doctors. *Br Med J* 1980;i:967–71.

6 Kannel WB, McGee DL, Castelli WP. Latest perspectives on cigarette smoking and cardiovascular disease: the Framingham Study. *J Card Rehabil* 1984;4: 267–77.

7 Willett WC, Green A, Stampfer MJ, *et al.* Relative and absolute excess risks of coronary heart disease among women who smoke cigarettes. *N Engl J Med* 1987; 317:1303–9.

8 Criqui MH, Cowan LD, Tyroler HA, *et al.* Lipoproteins as mediators for the effects of alcohol consumption and cigarette smoking on cardiovascular mortality: results from the Lipid Research Clinics Follow-up Study. *Am J Epidemiol* 1987;126:629–37.

9 Solberg LA, Strong JP. Risk factors and atherosclerotic lesions. A review of autopsy studies. *Arteriosclerosis* 1983;3:187–98.

10 Khan AH, Haywood LJ. Myocardial infarction in nine patients with radiologically patent coronary arteries. *N Engl J Med* 1974;291:427–31.

11 McKenna WJ, Chew CYC, Oakley CM. Myocardial infarction with normal coronary angiogram. Possible mechanism of smoking risk in coronary artery disease. *Br Heart J* 1980;43:493–8.

12 Aronow WS, Kaplan NM. Smoking. In: Kaplan NM, Stamler J, eds. *Prevention of coronary heart disease. Practical management of the risk factors*. Philadelphia: WB Saunders, 1983:51–60.

13 Wilhelmsen L, Svärdsudd K, Korsan-Bengsten K, Larsson B, Welin L, Tibblin G. Fibrinogen as a risk factor for stroke and myocardial infarction. *N Engl J Med* 1984;**311**:501–5.

14 Kannel WB, D'Agostino RB, Belanger AJ. Fibrinogen, cigarette smoking, and risk of cardiovascular disease: insights from the Framingham Study. *Am Heart J* 1987;**113**:1006–10.

15 Ernst E, Hammerschmidt DE, Bagge U, Matrai A, Dormandy JA. Leukocytes and the risk of ischemic diseases. *JAMA* 1987;**257**:2318–24.

16 Pearson TA. Coronary arteriography in the study of the epidemiology of coronary artery disease. *Epidemiol Rev* 1984;**6**:140–66.

17 Hartz AJ, Barboriak PN, Anderson AJ, Hoffman RG, Barboriak JJ. Smoking, coronary artery occlusion, and nonfatal myocardial infarction. *JAMA* 1981;**246**: 851–3.

18 Herbert WH. Cigarette smoking and arteriographically demonstrable coronary artery disease. *Chest* 1975; **67**:49–52.

19 Vlietstra RE, Kronmal RA, Frye RL, Seth AK, Tristani FE, Killip T III. Factors affecting the extent and severity of coronary artery disease in patients enrolled in the Coronary Artery Surgery Study. *Arteriosclerosis* 1982;**2**:208–15.

20 Willerson JT. Selection of patients for coronary arteriography. *Circulation* 1985;72(suppl V):V3–8.

21 Zir LM, Miller SW, Dinssmore RE, Gilbert JP, Harthorne JW. Interobserver variability in coronary angiography. *Circulation* 1976;**53**:627–32.

22 Fisher CM. Correlation of antemortem angiography with pathology. In: Bond MG, Insull W Jr, Glagov S, Chandler AB, Cornhill JF, eds. *Clinical diagnosis of atherosclerosis. Quantitative methods of evaluation.* New York: Springer-Verlag, 1983:265–82.

23 Freedman DS, Gruchow HG, Anderson AJ, Rimm AA, Barboriak JJ. Relation of triglyceride levels to coronary artery disease: The Milwaukee Cardiovascular Data Registry. *Am J Epidemol* 1988;**127**:1118–30.

24 Rowe GG, Thomsen JH, Sternlund RR, McKenna DH, Sialer S, Corliss RJ. A study of hemodynamics and coronary blood flow in man with coronary artery disease. *Circulation* 1969;**39**:139–48.

25 Block WD, Jarrett KJ Jr, Levine JB. Use of a single color reagent to improve the automated determination of serum total cholesterol. In: Skeggs LT Jr, ed. *Automation in analytical chemistry. Technicon symposia 1965.* New York: Mediad, 1966:345–7.

26 Kessler G, Lederer H. Fluorometric measurement of triglycerides. In: Skeggs LT Jr, ed. *Automation in analytical chemistry. Technicon symposia 1965.* New York: Mediad, 1966:341–4.

27 Manual of Laboratory Operation, Lipid Research Clinics Program. Vol. 1. Bethesda, Md: National Institutes of Health, 1974; DHEW publication no. (NIH) 75–628.

28 Tretli S, Land-Larsen PG, Foss OP. Reliability of questionnaire information of cardiovascular disease and diabetes: Cardiovascular Disease Study in Finnmark county. *J Epidemiol Community Health* 1982;**36**:269–73.

29 Åberg H, Lithell H, Selinus I, Hedstrand H. Serum triglycerides are a risk factor for myocardial infarction but not for angina pectoris. Results from a 10-year follow-up of Uppsala Primary Preventive Study. *Atherosclerosis* 1985;**54**:89–97.

30 Kleinbaum DG, Kupper LL, Morgenstern H. *Epidemiologic research. Principles and quantitative methods.* Belmont, Ca: Wadsworth, 1982:331–51.

31 Kleinman JC, Feldman JJ, Monk MA. Trends in smoking and ischemic heart disease mortality. In: Havlik RJ, Feinleib M, eds. *Proceedings of the conference on the decline in coronary heart disease mortality.* Bethesda, Md: National Institutes of Health, 1979 (NIH publication no. 79-1610): 195–211.

32 Schlesselman JJ. *Case-control studies.* New York: Oxford University Press, 1982:241–4.

33 Rosenberg L, Kaufman DW, Helmrich SP, Shapiro S. The risk of myocardial infarction after quitting smoking in men under 55 years of age. *N Engl J Med* 1985;**313**:1511–4.

34 McGill HC Jr. The cardiovascular pathology of smoking. *Am Heart J* 1988;**118**:250–7.

35 Wilhelmsson C, Vedin JA, Elmfeldt D, Tibblin G, Wilhelmsen L. Smoking and myocardial infarction. *Lancet* 1975;**i**:415–20.

36 Vlietstra RE, Kronmal RA, Oberman A, Frye RL, Killip T III. Effect of cigarette smoking on survival of patients with angiographically documented coronary artery disease. Report from the CASS Registry. *JAMA* 1986;**255**:1023–7.

37 Barry J, Mead K, Nabel EG, *et al.* Effect of smoking on the activity of ischemic heart disease. *JAMA* 1989; **261**:398–402.

38 Fitzgerald GA, Oates JA, Nowak J. Cigarette smoking and hemostatic function. *Am Heart J* 1988;**115**: 267–71.

39 Fried LP, Moore RD, Pearson TA. Long-term effects of cigarette smoking and moderate alcohol consumption on coronary artery diameter. Mechanisms of coronary artery disease independent of atherosclerosis or thrombosis? *Am Heart J* 1986;**80**:37–44.

40 Kuller L, Meilahn E, Ockene J. Smoking and coronary heart disease. In: Connor WE, Bristrow JD, eds. *Coronary heart disease: prevention, complications, and treatment.* Philadelphia: JB Lippincott, 1985:65–84.

Br Heart J 1989;62:281–3

Superior QRS axis in ventricular septal defect

N J SHAW,* M J GODMAN,* A HAYES,† G R SUTHERLAND†

From the Royal Hospital for Sick Children, Edinburgh, and †Southampton General Hospital, Southampton

SUMMARY The relation between the superior orientation of the QRS axis and the anatomical site of the defect in the ventricular septum in patients with a ventricular septal defect was studied. Of 1031 patients with a ventricular septal defect, 64 (6·2%) had a superior axis on their electrocardiogram. In 59% of these patients the defect was in the inlet portion of the ventricular septum or affected this area. None of the cases was classified as an isolated ventricular septal defect of the persistent atrioventricular canal type.

While there is an association between a superior axis and perimembranous inlet ventricular septal defect, a superior QRS axis does not characterise a ventricular septal defect as being of the atrioventricular canal type.

Superior orientation of the QRS axis was seen in 15% of patients with the clinical features of a ventricular septal defect[1] and this feature is claimed by some to characterise the site of the defect as likely to be in the posterior or inlet part of the septum.[2] More specifically, it has been suggested that a superior QRS axis is particularly associated with isolated ventricular septal defects of the "atrioventricular canal type".[2-4]

There is difficulty in determining with certainty from these earlier reports whether the ventricular septal defects referred to were truly of the "atrioventricular canal type"—if they were, the high incidence of left axis deviation is not unexpected. On the other hand, Anderson *et al* have suggested that these defects are more correctly termed perimembranous inlet ventricular septal defects.[5]

We studied the relation between superior orientation of the QRS axis and the anatomical site of the defect in the ventricular septum in patients with a ventricular septal defect to see whether a ventricular septal defect associated with a superior axis was likely to be of the "atrioventricular canal type".

Patients and methods

One thousand and thirty one electrocardiograms of patients diagnosed as having an isolated ventricular septal defect who had attended the Department of Cardiology at the Royal Hospital for Sick Children, Edinburgh, and the Paediatric Cardiology Unit, Southampton General Hospital, from 1970 to 1986 were reviewed. Those having an axis of − 1° to − 180° were defined as having a superior orientation of the QRS axis.[6 7]

In those with a superior axis, cross sectional echocardiography, Doppler studies, previous angiograms, or previous operation notes were used to identify the anatomical site of each ventricular septal defect. The classification of ventricular septal defects was based on that proposed by Soto *et al*[8] and modified by Sutherland *et al* for the echocardiographic diagnosis of ventricular septal defects.[9] The angiographic differentiation of types of ventricular septal defects was as proposed by the Birmingham Alabama Group, which showed that with axial views an experienced angiographer can define the location, size, and relations of ventricular septal defects with high accuracy.[10 11]

Results

Sixty four patients (6·2%) had a superior axis on their electrocardiogram, and this ranged from − 10° to − 100°. We were able to study 59 of these patients.

In 25 patients the site of the ventricular septal defect was identified by cross sectional echocardiography together with inspection of previous angiograms or operation notes and in 27 the site was identified by review of previous angiograms or operation notes or both. The remaining seven had normal cross sectional echocardiograms with no defect visualised nor any feature that identified a defect as having been present and subsequently

Requests for reprints to Dr M J Godman, Cardiology Department, Royal Hospital for Sick Children, Sciennes Road, Edinburgh EH9 1LF.

Accepted for publication 20 April 1989

undergone spontaneous closure. A muscular ventricular septal defect was confirmed in three of these seven cases by Doppler study and in the remaining four a muscular ventricular septal defect was assumed to have been present because of the quality and site of the murmur previously heard on auscultation.

The table shows the distribution of defects by site in those patients with a superior axis on their electrocardiogram. In one patient, in whom only angiographic studies were available, the defect was seen in the perimembranous region but it was impossible to define its extent because of the poor quality of the angiographic films.

In three of the 32 patients who had cross sectional echocardiography the defect had closed by the time of examination. In a further 11, all with an inlet component to the defect, there was tricuspid valve tissue adhering to the margins of the defect; in all these patients the clinical course suggested this may have been a mechanism by which the defect had become smaller. In 34 of the 59 patients with a ventricular septal defect and superior axis (shown in the table) the defect was in or affected the inlet septum and in 24 patients it did not ($\chi^2 = 14·30$ $p < 0·001$).

Discussion

We found that 65 (6·2%) of 1031 patients with a ventricular septal defect had a superior orientation of the QRS axis on their electrocardiogram; but Pryor and Blount found this feature in 15% of patients with a ventricular septal defect.[1] In 59% (35 of the 59 patients (table) of those with a superior orientation of the QRS axis the defect was in the inlet portion of the ventricular septum or affected this area; this includes one patient whose perimembranous defect was not clearly defined although it seemed to extend into the inlet septum. In a previous study of 280 children with ventricular septal defects who were classified without reference to the orientation of the QRS axis only 29% had a defect affecting or in the inlet portion of the septum.[9] Our findings therefore suggest that in patients with a ventricular septal defect who have a superior QRS axis the defect is most likely to lie in or affect the inlet portion of the ventricular septum ($\chi^2 = 14·30$, $p < 0·001$). This is perhaps not surprising in view of the proximity of the penetrating bundle of the atrioventricular conduction tissues to the inlet portion of the septum and the position of the branching bundle between the membranous and muscular septa.

Table *Distribution of ventricular septal defect by site in patients with superior orientation of the QRS axis*

Site	*Number*
Perimembranous confluent	16
Perimembranous confluent + muscular	1
Perimembranous (extent not known)	1
Perimembranous confluent + muscular + gerbode	1
Perimembranous inlet	15
Perimembranous inlet + apical trabecular + muscular inlet	1
Perimembranous outlet	7
Perimembranous outlet + muscular inlet	1
Muscular inlet	4
Muscular outlet	1
Muscular trabecular	10
Gerbode	1
Total	59

On the other hand, our study also indicated that the inlet ventricular septum is not affected in 41% of those patients with a ventricular septal defect who have superior orientation of the QRS axis. In these patients the ventricular septal defect lay in various sites in the perimembranous or muscular septum, although none was associated with a doubly committed subarterial defect. The mechanism by which the superior axis is produced in those patients is speculative. Sharrat and Virmani found left axis deviation in about 1% in normal children[12] and Shinebourne *et al* found it in 1·6% of patients with acyanotic heart disease other than that caused by an atrioventricular canal.[6] Fox *et al* reported left axis deviation in 40% of patients with multiple ventricular septal defects but did not describe the site of the defects in these patients nor were they able to offer any clear explanation for the high frequency of left axis deviation that they found.[13]

None of the patients was classified as having an isolated ventricular septal defect of the persistent atrioventricular canal type. Neufeld *et al* described 15 patients with a ventricular septal defect in whom the defect appeared to occupy a position similar to that of the ventricular component of a persistent common atrioventricular canal.[2] In all 15 patients the electrocardiographic findings were striking in that the mean QRS axis lay above the isoelectric point. Their's was a necropsy study with 15 (5%) of 300 ventricular septal defects being classified as the atrioventricular canal type.

It might seem surprising therefore that we did not identify any defects of the type reported by Neufeld *et al.* This difference may be apparent rather than real. Anderson *et al* suggested that the term "atrioventricular canal type of ventricular septal defect" is confusing, particularly when used to describe defects that they believe are more correctly termed "perimembranous inlet ventricular septal defects."[5] They emphasise that the defects often referred to in published reports as isolated ventricular septal defects of the atrioventricular type have none of the characteristics of the anomalies grouped together as atrioventricular septal defects.

We accept that some perimembranous inlet defects show the signs of atrioventricular defects, but no patient in our study had such features and we agree with the opinion that "isolated atrioventricular canal defect" is rare (Soto *et al*,[8] Becker and Anderson[14]).

A superior QRS axis therefore does not characterise a ventricular septal defect as being of the atrioventricular canal type. While there is an association between a superior axis and perimembranous inlet ventricular septal defect, almost half of all patients with such an axis will have the defect at a site other than the perimembranous inlet septum.

References

1 Pryor R, Blount SG. The clinical significance of true left axis deviation. *Am Heart J* 1966;72:391–413.

2 Neufeld HN, Titus JL, DuShane JW, Burchell HB, Edwards JE. Isolated ventricular septal defects of the persistent common atrioventricular canal type. *Circulation* 1961;23:685–96.

3 Perloff JK, Roberts NK, Cabeen WR Jr. Left axis deviation. *Circulation* 1979;60:12–21.

4 Toscana-Barbosa E, Brandenburg RO, Burchell HB. Electrocardiographic studies of cases with intracardiac malformations of the atrioventricular canal. *Mayo Clin Proc* 1956;31:513–23.

5 Anderson RH, Becker AE, Lucchese FE, Meier MA, Rigby ML, Soto B. *Morphology of congenital heart disease.* Kent: Castle House Publications, 1983:23–35.

6 Shinebourne EA, Haworth SG, Anderson RH, Ulgur A. Differential diagnosis of congenital heart disease in the first three months of life. *Arch Dis Child* 1974;49:729–33.

7 Liebman J, Nada AS. An abnormally superior vector (formerly called marked left axis deviation). *Am J Cardiol* 1971;27:577–80.

8 Soto B, Becker AE, Moulaert AJ, Lie JT, Anderson RH. Classification of ventricular septal defects. *Br Heart J* 1980;43:332–43.

9 Sutherland GR, Godman MJ, Smallhorn JF, Guiterras P, Anderson RH, Hunter S. Ventricular septal defects. Two dimensional echocardiographic and morphological correlations. *Br Heart J* 1982;47:316–28.

10 Elliot LP, Bargeron LM, Soto B, Brown BR. Axial cine angiography in congenital heart disease. *Radiol Clin North Am* 1980;18:515–23.

11 Santamaria H, Soto B, Ceballos R, Bargeron LM, Coghlan HC, Kirklin JW. Angiographic differentiation of types of ventricular septal defects. *Am J Roentgenol* 1983;141:273–81.

12 Sharrat GP, Virmani S. Left axis deviation in otherwise healthy children. *Pediatr Cardiol* 1985;6:7–10.

13 Fox KM, Patel GR, Graham GR, *et al.* Multiple and single ventricular septal defect—a clinical and haemodynamic comparison. *Br Heart J* 1978;40:141–6.

14 Becker AE, Anderson RH. *Pathology of congenital heart disease.* (Postgraduate pathology series.) Butterworths, 1981:93–117.

Br Heart J 1989;62:284–90

Doppler flow characteristics in the assessment of pulmonary artery pressure in ductus arteriosus

A B HOUSTON, M K LIM, W B DOIG, J GNANAPRAGASAM, E N COLEMAN,
M P G JAMIESON, J C S POLLOCK

From the Departments of Cardiology, Cardiac Surgery, and Child Health, Royal Hospital for Sick Children, Glasgow

SUMMARY The Doppler spectral pattern of flow through the ductus arteriosus was studied in 117 patients. In 37 who underwent catheterisation, Doppler records and aortic and pulmonary artery pressure were available (21 simultaneously with two catheters) for review while the others had surgical ligation of the duct on the basis of the results of non-invasive tests. Four flow patterns were obtained: (*a*) continuous flow, maximum velocity in late systole with gradual fall throughout diastole; (*b*) continuous flow, high systolic flow with rapid fall to a very low early diastolic velocity maintained throughout diastole; (*c*) continuous low velocity, maximum in late diastole; and (*d*) bidirectional flow. Flow pattern (*a*) was associated with normal or slightly raised pulmonary artery pressure; (*b*) with raised pulmonary artery pressure; and (*c*) and (*d*) with pulmonary artery pressure at systemic values. Comparison of the Doppler and measured pressure differences between the great arteries was reasonably good for peak values but poor for the trough readings.

Doppler ultrasound clearly showed ductal flow; the flow pattern gave an indication of the pulmonary artery pressure, but pressure measurement by application of the Bernoulli equation to the flow velocities cannot yet be regarded as reliable.

The diagnosis of ductus arteriosus is usually readily apparent on clinical examination but may be difficult where the murmur is obscured by another louder one or is unrecognisable or atypical because of pulmonary hypertension[1]; and echocardiography is of limited value in confirming its presence.[2] In addition, where expertise in surgery of infants is not available patients may not undergo ductus ligation routinely until after the second year of life; it is then essential to be able to assess the pulmonary pressure to select those who need earlier closure. Doppler ultrasound has the potential to show and measure the velocity of ductal flow and may thus be of practical value in patient management by determining the pulmonary artery pressure or confirming the diagnosis where there is difficulty with either clinical or echocardiographic assessment.

Ductal flow can be shown with pulsed[3] and continuous wave[4] Doppler; and colour Doppler flow mapping[5] outlines the ductus when it is difficult to image with echocardiography. In most cases a signal showing continuous flow throughout the cardiac cycle is clearly recognised, but the flow pattern may be atypical when the usual pressure differences between the great arteries do not occur. It has been reported that the flow pattern changes with pulmonary artery hypertension[6] and that the pulmonary pressure can be predicted from the application of the Bernoulli equation[7] to the ductal flow velocity.[4] While one recent study reported difficulties in determining the pressure drop between the great arteries[8] from the Bernoulli equation, another found this to be satisfactory.[9] Although these studies reported on a total of 55 individuals only six were investigated with dual catheter pressure measurements and no attention was given to the possible differences between the peak to peak and trough to trough and instantaneous maximum and minimum pressure differences.

We found that pulmonary pressure cannot always be predicted reliably and that the flow patterns may be of more value for assessing pulmonary pressure. Thus we now report our experience with Doppler ultrasound in patients with a ductus arteriosus undergoing cardiac catheterisation or surgical ligation, with particular reference to the difference

Requests for reprints to Dr A B Houston, Royal Hospital for Sick Children, Yorkhill, Glasgow G3 8SJ.

Accepted for publication 31 March 1989

between the instantaneous and peak to peak measured pressures, the variability in the spectral flow patterns, and the use of the spectral signal to attempt to calculate the pulmonary artery pressure by the application of the Bernoulli equation.

Patients and methods

Patients with a ductus dependent circulation such as preductal coarctation were excluded. Between August 1985 and September 1988, 159 other patients (aged two days to 14 years) with a ductus arteriosus underwent either cardiac catheterisation (40) or direct surgical closure (119) on the basis of clinical and non-invasive studies.

The Doppler spectral recordings and pulmonary arterial and aortic pressures at catheterisation were available for review in 37 children (aged two days to 15 years, mean 3·5 years). The pressures were measured through fluid filled catheters attached to strain gauge transducers that were initially matched as closely as possible with both catheters in the same chamber. Pressures were measured through two catheters (21) or by withdrawal of a single catheter (16) from the descending aorta to the main pulmonary artery. In three in whom an arterial approach was used for the second catheter the aortic pressure was measured with it in the arch; a second venous catheter was passed through the pulmonary artery into the descending aorta in the others. The Doppler study was performed simultaneously with the pressure recordings in 27, including 20 studied with two catheters.

Of these 37, 16 had an isolated ductus arteriosus, three a recanalised ductus, seven a ventricular septal defect, two mitral valve disease, two an atrial septal defect, two peripheral pulmonary artery stenosis, one cardiomyopathy, one a right ductus arteriosus, one a pulmonary artery sling, one aortic stenosis, and one an atrioventricular canal with total anomalous pulmonary venous drainage.

Thirty of those not catheterised were preterm infants with respiratory distress syndrome, and Doppler studies were not routinely performed; they have not been considered in the analysis of the results. Doppler records were available in 80 of the 89 other patients.

Thus simultaneous Doppler and catheter data were available in 27 (20 measured with two catheters), non-simultaneous Doppler and catheter data in 10, and Doppler measurements alone in 80 undergoing operation without catheterisation. Dual catheter pressures were available in 21, in one of whom simultaneous Doppler data were not available.

The early Doppler studies were performed with a non-imaging Alfred velocimeter (Vingmed) interfaced to a Doptek spectrum analyser and later ones, after January 1987, with a Vingmed CFM 700 system with imaging and colour flow mapping. With imaging and colour Doppler a short axis view of the great arteries was used and the beam was aligned in the distal main pulmonary artery where ductal flow was apparent. Because the maximum velocity signal may be obtained from another site we sought it from the first, second, and third left interspaces and the suprasternal notch, using the stand alone transducer when necessary. With the non-imaging system the signal was usually obtained easily with continuous wave Doppler and the stand alone transducer by interrogating the same positions. The maximum and minimum frequency shifts were measured from the Doppler signal. From these we derived the maximum and minimum velocities (V) and estimated the pressure drops (P) from the modified Bernoulli formula, $P = 4V^2$.

Of the 117 available Doppler studies the stand alone system was used in 48 (25 undergoing catheterisation) and the duplex colour flow system in 69 (12 undergoing catheterisation).

The spectral tracings were analysed to review both the timing and patterns of the signals in systole and diastole. The maximum velocity in systole and the minimum velocity in diastole were then measured and the maximum and minimum pressure differences between the great arteries calculated by the modified Bernoulli equation.[7] The Doppler and catheterisation pressure gradients between the great arteries were then compared for both the maximum pressure differences in systole and the minimum differences in diastole, the differences between them being analysed by the method of Bland and Altman.[10] Study of the waveforms suggested that higher pulmonary artery pressure was associated with an increase in the ratio of the systolic to diastolic flow velocity. Thus in addition to measuring this ratio with Doppler, we also calculated the ratio from the measured pressure differences by translating their values in mm Hg into m/s, as would be measured with Doppler if the Doppler and catheter gradients were exactly equal.

The pressure tracings were also analysed to measure the instantaneous maximum and minimum gradients and to compare them with peak to peak and trough to trough gradients respectively.

Results

PRESSURE MEASUREMENTS AT CATHETERISATION BY TWO CATHETERS

Three infants in whom the differences between the aortic and pulmonary pressures was greatest in diastole when they were studied with two catheters (see figs 3 and 4) were excluded in this analysis. In the other 18 studied with two catheters the peak to peak gradients in systole ranged from 28 to 116 mm Hg and instantaneous ones from 34 to 124 mm Hg. The difference was greater than 10 mm Hg in only two (14 and 16 mm Hg) with mean (2 SD) of 6·7 (8·3). Similarly the trough to trough gradients in diastole ranged from 0 to 83 mm Hg and the instantaneous minimum from 0 to 79 mm Hg. The maximum difference was 11 mm Hg with mean (2 SD) of 5·6 (7·2).

DOPPLER FLOW PATTERNS IN CATHETERISED PATIENTS

The flow patterns in the 37 patients showed variation in the timing of and relative values of the maximum and minimum velocities in systole and diastole. Inspection of the tracings showed four different flow patterns:

(a) Continuous flow: maximum velocity in late systole with a gradual fall throughout diastole (26 of the 37)
The ductus arteriosus signal characteristically showed continuous flow (fig 1a) with maximum velocity in late systole, ranging from 3·3 to 4·7 (mean 4·1) m/s, equivalent to a gradient of 44 to 88 mm Hg. The velocity signal then fell gradually to its lowest value just after the R wave, often showing an abrupt dip before the rapid rise to its maximum. The lower velocity was still clearly discernible, being above 1·5 m/s, ranging from 1·5 to 3·5 (mean 2·5) m/s, equivalent to a pressure drop of 9–50 mm Hg. The ratio of systolic to diastolic velocities was from 1·3 to 2·4 (mean (SD) 1·6 (0·3)) (two of 2·4 others $\leqslant$ 2·1). These patients had a relatively high pressure difference between the great arteries throughout the cardiac cycle (fig 1a): the pulmonary artery systolic pressure was <50 mm Hg (20–30 in six, 31–40 in 17, 41–50 in three, and the diastolic pressure was $\leqslant$ 30 mm Hg (0–10 in five, 11–20 in 15, 21–30 in six).

(b) Continuous flow: high systolic velocity with rapid fall to a very low early diastolic velocity that was maintained throughout diastole (seven of the 37)
The systolic signal was of relatively high velocity (equivalent to a pressure difference of 16–50 mm Hg) falling rapidly at end systole to a relatively low velocity (<1·0 m/s) that was maintained throughout diastole (fig 2a). The measured pressures in diastole in the aorta and pulmonary artery were virtually equal (fig 2b). Pulmonary systolic pressures were all >50 mm Hg (52–88 mm Hg) and the diastolic ones above 30 mm Hg (32–51 mm Hg). The ratio of systolic to diastolic velocities ranged from 2·0 to 5·0 (mean (SD) 3·4 (1·1)) (one of 2·0 others $\geqslant$ 2·9).

Consideration of the 33 with flow patterns a and b showed that all but one of the 27 with a ratio of <2·5 had a pulmonary pressure of <50 mm Hg in systole and 30 mm Hg in diastole, and all six with a ratio >2·8 had pressures >50 and 30 mm Hg during systole and diastole respectively. When the catheter gradients in mm Hg were translated into velocity in m/s and the ratio calculated it was <1·6 in all with pulmonary pressure <50/30 mm Hg and higher than this in the seven with higher pulmonary pressure (1·7, 1·9, 2·5, 2·9, 3·1, and infinity in two).

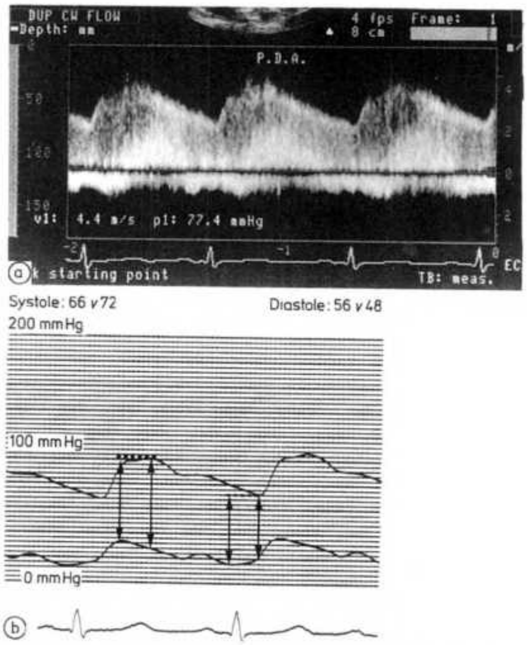


Fig 1 *Records from a patient with normal pulmonary artery pressure. The continuous wave (CW) Doppler signal (a) shows velocity reaching a maximum in late systole and falling to a minimum just after the R wave. The pressure record (b) shows that the pressure difference between the arteries mirrors this pattern and remains relatively large throughout the cardiac cycle. Note the difference between the instantaneous maximum and minimum gradients and the peak to peak and trough to trough values.*

(c) Continuous low velocity flow, maximum in late diastole
In one infant with a ventricular septal defect and ductus arteriosus the spectral signal showed continuous low velocity flow but with the maximum velocity (1·6 m/s) late in diastole and the minimum one at end systole (fig 3a). Simultaneously measured pressures (fig 3b) showed a raised pulmonary pressure (60/20 mm Hg) with the pressure difference between the great arteries altered such that it was

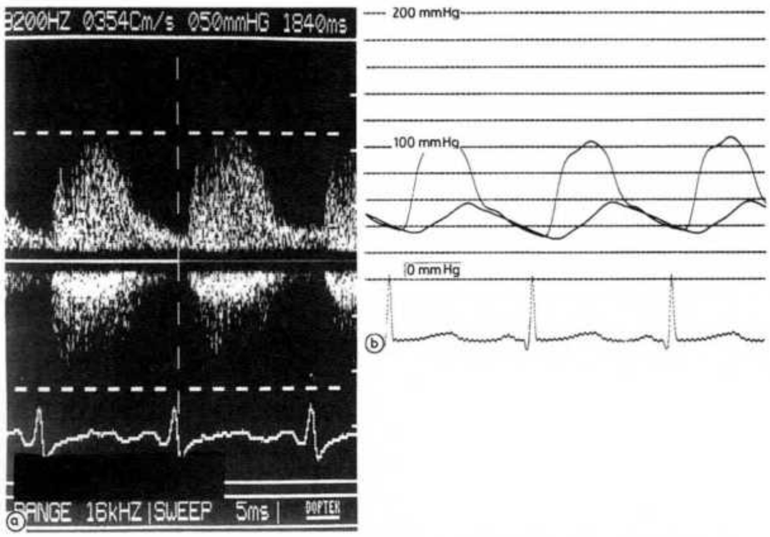

[redacted]

Fig 2 *Records from a patient with raised pulmonary artery pressure. The signal of continuous wave Doppler (a) shows maximum velocity in late systole and falls rapidly to a relatively low diastolic velocity, which also reaches its minimum just after the R wave. The pressure record (b) shows that the pressure difference between the arteries mirrors this pattern being high in systole but virtually absent in diastole.*

greatest in late diastole and early systole, and least in mid to late systole.

(*d*) *Bidirectional flow*

In three infants with pulmonary artery pressure at approximately systemic values the Doppler signal showed bidirectional flow—from the pulmonary artery to the aorta in systole and in the opposite direction in diastole. At catheterisation two had pulmonary artery hypertension (equivalent to systemic pressure) with ventricular septal defects (multiple in one) and large left to right shunts. Doppler showed flow from the pulmonary artery to the aorta for a short time in systole, with aorta to pulmonary artery flow throughout the rest of the cardiac cycle (fig 4a) and in the infant studied with two catheters simultaneous pressure recordings (fig 4b) showed that pressure in the pulmonary artery was higher than in the aorta for a short time in mid systole; pressure in the aorta was higher for the rest of the cardiac cycle. In the third, a two day old infant with dilated cardiomyopathy catheterised to exclude an anomalous coronary artery, flow from the pulmonary artery to aorta measured by Doppler lasted almost as long as flow from the aorta to pulmonary artery. The pressure tracing during withdrawal of the catheter indicated that the pulmonary artery pressure was higher in systole and lower in diastole than that in the aorta; this Doppler appearance is similar to that in other patients with persistent fetal circulation who cannot be included in this series.

DOPPLER WAVEFORMS IN PATIENTS WHO WERE NOT CATHETERISED

Of the 80 patients in whom Doppler studies were available the waveform showed a slow fall with a relatively high diastolic velocity in 71 (as in fig 1), while eight showed a sharp fall with a low velocity throughout diastole (as in fig 2) and one showed bidirectional flow.

COMPARISON OF DOPPLER AND SIMULTANEOUS MEASURED GRADIENTS

The three infants with pulmonary to aortic flow in systole (fig 4) were excluded in this assessment, leaving a total of 24 patients studied at catheterisation. In 18 of those dual catheter studies were performed and instantaneous gradients could be measured.

The method of Bland and Altman[10] showed that the difference between the Doppler and peak to peak maximum gradients (n = 24) ranged from −20 to 22 mm Hg with mean (2 SD) of 1·6 (24·1) mm Hg (fig 5, top), while the difference between the minimum and trough values ranged from −40 to +9, mean −13·6 (24·9) mm Hg (fig 5, bottom). When Doppler values were compared with instantaneous maximum values (n = 18) the mean (2 SD) was −7·9 (30·6) and

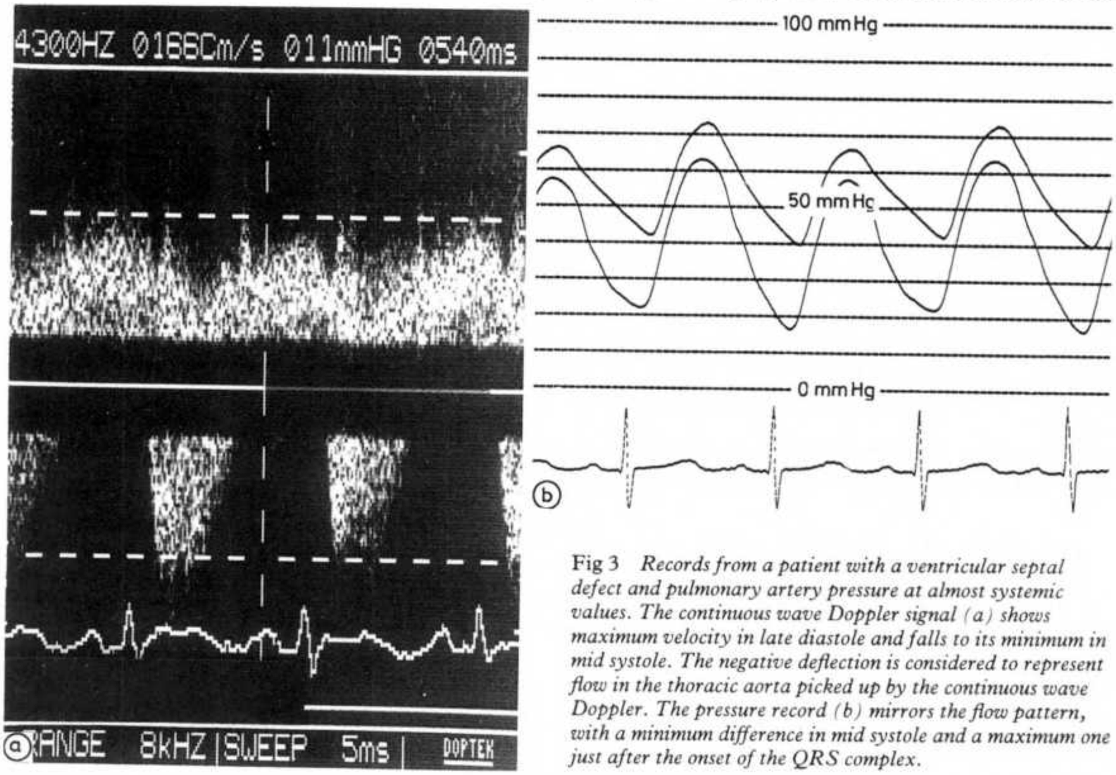


Fig 3 *Records from a patient with a ventricular septal defect and pulmonary artery pressure at almost systemic values. The continuous wave Doppler signal (a) shows maximum velocity in late diastole and falls to its minimum in mid systole. The negative deflection is considered to represent flow in the thoracic aorta picked up by the continuous wave Doppler. The pressure record (b) mirrors the flow pattern, with a minimum difference in mid systole and a maximum one just after the onset of the QRS complex.*

compared with instantaneous minimum values it was −11·3 (28·1).

Discussion

We found that Doppler ultrasound always detected ductal flow. It is important to be aware of the different waveforms found when pulmonary pressure is abnormal, because patients with an atypical murmur have the less common waveforms, and it is these patients in whom clinical examination may be uncertain. The most common signal (fig 1) is continuous, but the signal may have a sharp late systolic fall with a very low velocity throughout diastole (fig 2), a higher diastole than systolic velocity (fig 3), or show bidirectional flow (fig 4). The continuous signal (type a) is likely to be associated with a low or moderately raised pulmonary pressure (here systolic <50 mm Hg and diastolic <30 mm Hg) and the signal with sharp fall at end systole (type b) with a higher pressure. This distinction is not always an obvious one, is to an extent subjective, and does not allow a clear differentiation; a type b signal may simply represent a non-restrictive ductus. A signal showing a velocity higher in diastole than systole (type c) or bidirectional flow (type d) indicates pulmonary systolic pressure at approximately systemic values.

Since the waveform results from flow across the ductus it should reflect the pressure difference between the aorta and pulmonary artery, which was assessed by dual catheter studies in the ductus arteriosus by Spach *et al.*[11] They reported three types of pattern: (*a*) a continuous pressure drop and flow from the aorta to the pulmonary artery; the aortic pressure was higher throughout the cycle with maximum difference in systole and miminum at end diastole, just after the QRS complex; (*b*) bidirectional pressure gradient and flow (there was a pulmonary to aorta pressure gradient of brief duration during initial systole on the upstroke of the pressure curves or just before the peak of the aortic pressure, with an aorta to pulmonary gradient thereafter); (*c*) systemic circulation supplied by a ductus arteriosus with right to left shunt (aortic atresia) (in these ductus dependent patients there was a considerable right to left gradient until after the peak of the pulmonary artery pressure, with a left to right gradient throughout diastole).

All but four of our patients had a continuous aorta to pulmonary artery pressure gradient and flow, with maximum velocity in systole. Musewe *et al* divided their patients into those with continuous flow from

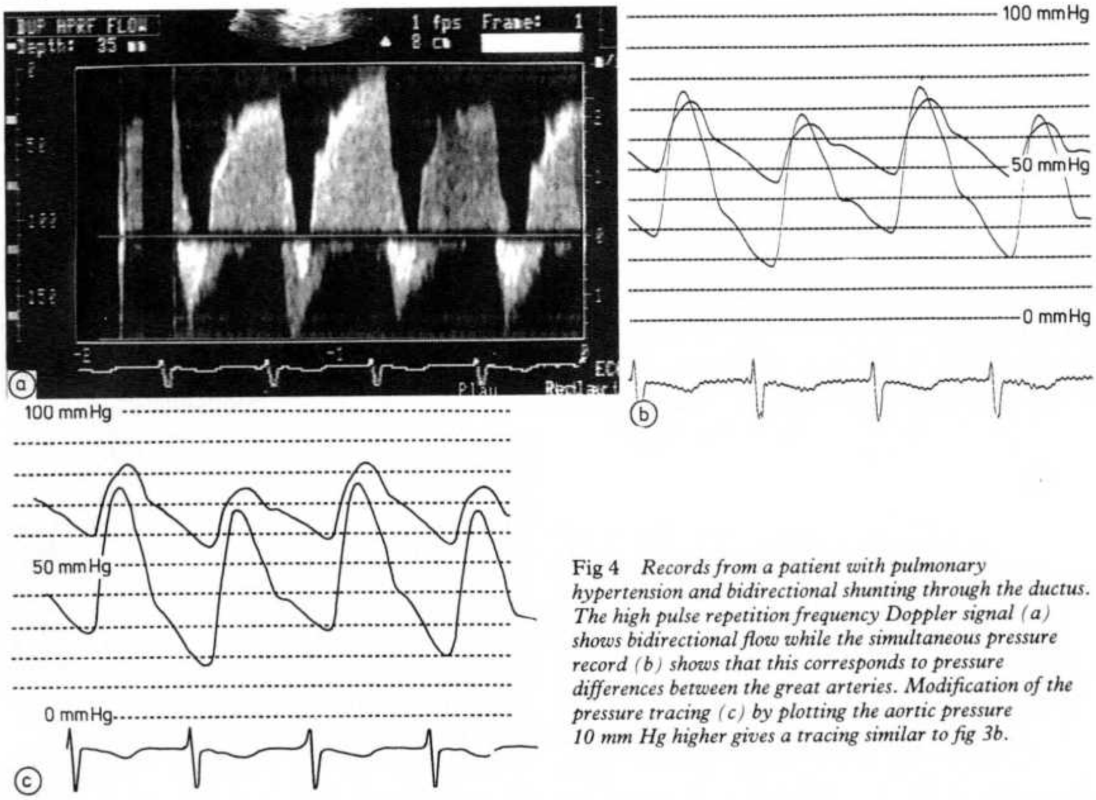


Fig 4 *Records from a patient with pulmonary hypertension and bidirectional shunting through the ductus. The high pulse repetition frequency Doppler signal (a) shows bidirectional flow while the simultaneous pressure record (b) shows that this corresponds to pressure differences between the great arteries. Modification of the pressure tracing (c) by plotting the aortic pressure 10 mm Hg higher gives a tracing similar to fig 3b.*

the aorta to the pulmonary artery and those with bidirectional shunting.[9] Spach *et al* did not comment on the pressure differences throughout the cardiac cycle between those with moderately raised and normal pulmonary artery pressure[11] and the differential suggested in this report is somewhat subjective. The ratio of maximum to minimum pressure gradient does not allow a clear distinction between high and low pulmonary artery pressure but it may be useful to regard a ratio of $\geqslant 2{\cdot}5$ as suggesting an important increase in pulmonary pressure although a lower one does not exclude an increased pulmonary pressure. Although the catheter studies showed a similar variation, a ratio of $\leqslant 1{\cdot}6$ was associated with lower pulmonary pressure. In addition, calculation of this ratio in the 26 measurements in infants with a ductus arteriosus reported by Rudolph *et al*[1] does not support this contention. This ratio is likely to be related to more complex haemodynamic findings than simply pulmonary artery pressure and further study is necessary to ascertain the true value of this ratio in the assessment of pulmonary artery pressure.

The presence of pulmonary artery pressure at systemic values produces a different signal, possibly with bidirectional shunting. Musewe *et al* reported that where there was continuous left to right shunting Doppler velocity reached a maximum later in the cardiac cycle with increasing pulmonary artery pressure[9]; the example in fig 3a presumably represents the extreme end of this, being maximum at the onset of the QRS complex. Although the waveforms in figs 3 and 4b initially seem different, study of the pressure signals shows that they both reflect similar pulmonary artery pressures, which are approximately equal to the aortic ones in systole and much less in diastole. Thus if the aortic pressure from fig 4b (which was described by Spach *et al* in patients with bidirectional pressure gradient and flow[11]) is plotted about 10 mm Hg higher (fig 4c) it gives a record similar to fig 3b. Patterns c and d are indications that the pulmonary pressure is approximately at systemic values, with d being the more severe, perhaps indicating increasing resistance.

It has been suggested that because the aortic pressure can be measured with a sphygmomanometer the Doppler gradient between the great arteries can be used to assess the pulmonary pressure in the ductus arteriosus.[4 9] This study, like that reported by Hiraishi *et al*,[8] found considerable variability between the measured gradients and Doppler gradients in both systole and diastole. Because those with very high pulmonary pressure

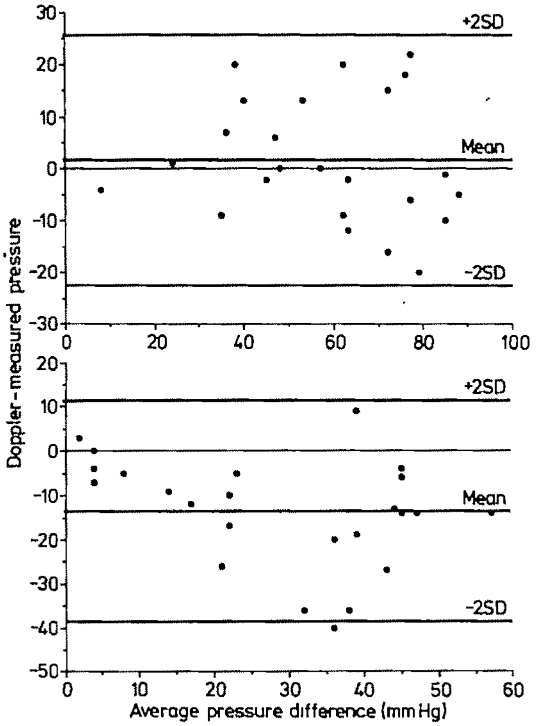


Fig 5 *Comparison of the difference in the Doppler and measured peak to peak (top) and trough to trough (bottom) pressures against the average of the measurements made simultaneously at the time of catheterisation.*

and abnormal flow were excluded from the analysis, this group is biased towards those with a relatively high pressure difference. But the results show both overestimation and underestimation, and in our hands the technique cannot yet be relied upon. Pressure underestimation may be the result of difficulty in aligning the Doppler beam and flow direction and many studies were performed without colour Doppler guidance. Furthermore, the transducer was adjusted to show the highest velocity systolic signal and the systolic and diastolic velocities were measured from it; it may be that an alteration in the flow direction in diastole resulted in a considerable underestimation of the diastolic gradient and particularly poor correlation in this study. In addition in some cases the spectral signal was of low intensity and this may be a further source of error.

This study indicates that Doppler ultrasound, stand alone spectral as well as duplex colour flow mapping, is a reliable means of showing the presence of a ductus arteriosus. It also suggests that Doppler may not accurately estimate the pulmonary artery pressure from the ductal flow signal. If Doppler is used to assess the pulmonary pressure we suggest that the flow pattern should be considered in addition to calculating the absolute pressures from the flow velocities. We conclude that the clinical accuracy and value of Doppler ultrasound in relation to other non-invasive means of assessing the pulmonary pressure are as yet unproved.

JG is supported by a grant from the Equipment Evaluation Committee of the Scottish Home and Health Department.

References

1 Rudolph AM, Mayer FE, Nadas AS, Gross RE. Patent ductus arteriosus. A clinical and hemodynamic study of 23 patients in the first year of life. *Pediatrics* 1958;22:892–903.

2 Wilson N, Dickinson DF, Goldberg SJ, Scott O. Pulmonary artery velocity patterns in ductus arteriosus. *Br Heart J* 1984;52:462–4.

3 Stevenson JG, Kawabori I, Guntheroth WG. Pulsed Doppler echocardiographic diagnosis of patent ductus arteriosus: sensitivity, specificity, limitations and technical features. *Cathet Cardiovasc Diagn* 1980;6: 255–63.

4 Hatle L, Angelsen B. *Doppler ultrasound in cardiology: physical principles and clinical applications.* Philadelphia: Lea and Febiger, 1985:220–8.

5 Swensson RE, Valder-Cruz LM, Sahn DJ, *et al.* Real-time Doppler color flow mapping for detection of patent arterial ductus. *J Am Coll Cardiol* 1986;8: 1105–12.

6 Stevenson JG, Kawabori I, Guntheroth WG. Non-invasive detection of pulmonary hypertension in patent ductus arteriosus by pulsed Doppler echocardiography. *Circulation* 1979;60:355–9.

7 Hatle L, Brubakk A, Tromsdal A, Angelsen B. Non-invasive assessment of pressure drop in mitral stenosis by Doppler ultrasound. *Br Heart J* 1978;40: 131–40.

8 Hiraishi S, Horiguchi Y, Misawa H, *et al.* Noninvasive Doppler echocardiographic evaluation of shunt flow dynamics of the ductus arteriosus. *Circulation* 1987; 75:1146–53.

9 Musewe NN, Smallhorn JF, Benson LN, Burrows PE, Freedom RM. Validation of Doppler-derived pulmonary arterial pressure in patients with ductus arteriosus under different hemodynamic states. *Circulation* 1987;76:1081–91.

10 Bland JM, Altman DG. Statistical methods for assessing agreement between two methods of clinical measurement. *Lancet* 1986;i:307–10.

11 Spach MS, Serwer GA, Anderson PAW, Canent RV, Levin AR. Pulsatile aortopulmonary pressure-flow dynamics of patent ductus arteriosus in patients with various haemodynamic states. *Circulation* 1980;61: 110–22.

Br Heart J 1989;62:291–7

Cross sectional echocardiographic anatomy of common atrioventricular valve in atrial isomerism

JUN ARISAWA,* SHIZUO MORIMOTO,* JUNPEI IKEZOE,* SEIKI HAMADA,* TAKAHIRO KOZUKA,* TETSUYA SANO,† MINORU OGAWA,† HIKARU MATSUDA,‡ YASUNARU KAWASHIMA‡

*From the Departments of *Radiology and †Paediatrics and ‡First Surgical Department, Osaka University Medical School, Osaka, Japan*

SUMMARY The morphology of the common atrioventricular valve and its relation to the ventricles was assessed by cross sectional echocardiography in 17 patients with atrial isomerism—four with left isomerism and 13 with right isomerism. In 13 patients the atrioventricular valve consisted of four leaflets: a large anterosuperior leaflet, two lateral leaflets, and a posteroinferior leaflet. The remaining four patients had two anterosuperior leaflets. Five patients had hearts with a double inlet right ventricle and all of them had a rudimentary left ventricle. All the commissures were attached to the right ventricle. Five patients showed severe right ventricular dominance. The atrioventricular morphology in these five hearts differed from that in the patients with the usual atrial arrangement, concordant atrioventricular connection, and hypoplasia of the left ventricle. Only the anterosuperior leaflet bridged the rudimentary left ventricle, and the posteroinferior leaflet was tethered to the ventricular septal crest. Six patients had a biventricular atrioventricular connection and two of them showed mild right ventricular dominance. The atrioventricular morphology in these hearts was the same as that seen in the patients with usual atrial arrangement and a concordant atrioventricular connection. The remaining patient showed dominance of the left ventricle. Only the anterosuperior leaflet bridged the rudimentary right ventricle in this heart.

Atrial isomerism is commonly associated with anomalies of venous drainage, atrioventricular connection, ventricular morphology, ventriculoarterial connection, and a pulmonary obstructive lesion.[1-3] In atrial isomerism a common atrioventricular valve is the most frequent mode of atrioventricular connection and the ventricular morphology is variable.[4] All types of heart with a double inlet ventricle are common in atrial isomerism.[4] A common atrioventricular valve was easily detected by cross sectional echocardiography in hearts with a double inlet ventricle.[5] The detailed echocardiographic detection of the position of attachment of the commissural chordae of the anterosuperior leaflets of the common atrioventricular valve in the hearts with the usual atrial arrangement and concordant atrioventricular connection has been reported.[6] But there is no clinical or pathological study to determine what part of the common atrioventricular valve is inserted into a rudimentary ventricle in a heart with a dominant ventricle or whether the shape of the common atrioventricular valve in the heart with atrial isomerism and a biventricular atrioventricular connection is the same as that in hearts with the usual atrial arrangement and concordant atrioventricular connection.

We used cross sectional echocardiography to study the common atrioventricular valve and its relation to the shape and size of the ventricle in hearts showing atrial isomerism.

Patients and methods

Seventeen patients with a common atrioventricular valve associated with thoracic isomerism were examined during a two year period from 1 March 1983 at Osaka University Medical School. Thoracic isomerism was identified by a plain chest radiograph and angiocardiography. Right isomerism was diag-

Requests for reprints to Dr Jun Arisawa, Department of Radiology, Osaka University Medical School, 1-1-50 Fukushima, Fukushima-ku, Osaka 553, Japan

Accepted for publication 20 April 1989

nosed if the chest radiograph showed bilateral short main bronchi and angiography showed bilateral eparterial bronchi. Left isomerism was diagnosed if there were bilateral long main bronchi and hyparterial bronchi. Atrial isomerism was confirmed by intraoperative examination of the atrial appendages in eight patients and at necropsy in two patients. The cardiac axis and ventricular morphology were identified by angiography. The relation of the ventricles to the common atrioventricular valve was established by both cross sectional echocardiography and ventriculography.

The patients were examined with a Hewlett-Packard sector scanner 77020A and a 3·5 or 5·0 MHz transducer in the apical and precordial four chamber views, precordial short axis view, and subcostal short axis view. We examined the number of leaflets, number of papillary muscles in the left ventricle, and the position of attachment of each commissural chorda in relation to ventricular morphology and the position of the trabecular ventricular septum.

Results

We identified left isomerism in four patients and right isomerism in 13 cases (table). The table also shows the position of the cardiac apex, the atrioventricular connection, the ventricular size, and the ventriculoarterial connection. Two ventricles were identified in all the patients. A morphologically right ventricle was situated anteriorly in 15 patients and posteriorly in two (cases 12 and 17) with right isomerism.

NUMBER OF LEAFLETS

In 13 of the 17 common atrioventricular valves four leaflets (anterosuperior, posteroinferior, and two lateral leaflets) were identified echocardiographically. Two anterosuperior leaflets were shown in another four patients (fig 1).

SHAPE OF LEAFLETS IN 10 PATIENTS WITH CONSIDERABLE RIGHT VENTRICULAR DOMINANCE

In five patients all the commissures were attached to the right ventricle (fig 1a and fig 2). In another five patients the anterosuperior leaflet bridged the rudimentary left ventricle, and the commissure between the left lateral leaflet (which was situated at the left ventricular side) and a posteroinferior leaflet was attached to the ventricular septal crest (figs 1b and 1c, fig 3).

ARRANGEMENT OF LEAFLETS IN SIX PATIENTS WITH MILD RIGHT VENTRICULAR DOMINANCE OR WITH BIVENTRICULAR ATRIOVENTRICULAR CONNECTION

In one of the two patients with mild right ventricular dominance we found two anterosuperior leaflets, and the commissure between these leaflets was attached to a papillary muscle on the right ventricular aspect of the anterior ventricular septum (fig 1d). The posteroinferior leaflet also bridged part of the left ventricle in this patient. In another patient the anterosuperior leaflet was free floating and both the anterior and posteroinferior leaflets straddled the interventricular septum (fig 1e).

Table *Position of cardiac apex, atrioventricular connection, ventricular size, and ventriculoarterial connection in 17 patients with atrial isomerism and common atrioventricular valve. The right ventricular chamber was posteriorly positioned in patients 12 and 17 and anteriorly in 15 patients*

Patient No	*Age*	*Sex*	*Type of isomerism*	*Position of cardiac apex*	*Atrioventricular connection and ventricular size*	*Ventriculoarterial connection*
1	6 mnth	F	Left	Left	Double inlet right ventricle	DORV, PS
2	5 yr	M	Left	Left	Biventricular A-V connection	Ao from RV, PA
3	11 yr	M	Left	Right	Right ventricular dominance	DORV, PS
4	2 yr	M	Left	Right	Biventricular A-V connection	Ao from RV, PA
5	6 yr	M	Right	Left	Double inlet right ventricle	Ao from RV, PA
6	1 yr	F	Right	Left	Double inlet right ventricle	Ao from RV, PA
7	8 yr	M	Right	Left	Double inlet right ventricle	DORV, PS
8	2 yr	F	Right	Left	Right ventricular dominance	DORV, PS
9	7 yr	M	Right	Left	Right ventricular dominance	DORV, PS
10	8 yr	F	Right	Left	Right ventricular dominance	DORV, PS
11	5 yr	M	Right	Left	Biventricular A-V connection	DORV, PS
12	4 yr	F	Right	Left	Biventricular A-V connection	Ao from RV, PA
13	4 mnth	M	Right	Right	Double inlet right ventricle	Ao from RV, PA
14	1 yr	M	Right	Right	Right ventricular dominance	Ao from RV, PA
15	3 mnth	M	Right	Right	Right ventricular dominance	DORV, PS
16	15 yr	F	Right	Right	Left ventricular dominance	TGA(1), PS
17	11 yr	F	Right	Right	Right ventricular dominance	DORV, PS

Ao, aorta; DORV, double outlet right ventricle; PA, pulmonary atresia; PS, pulmonary stenosis; RV, right ventricle; TGA(1), transposition of great arteries with left sided aorta

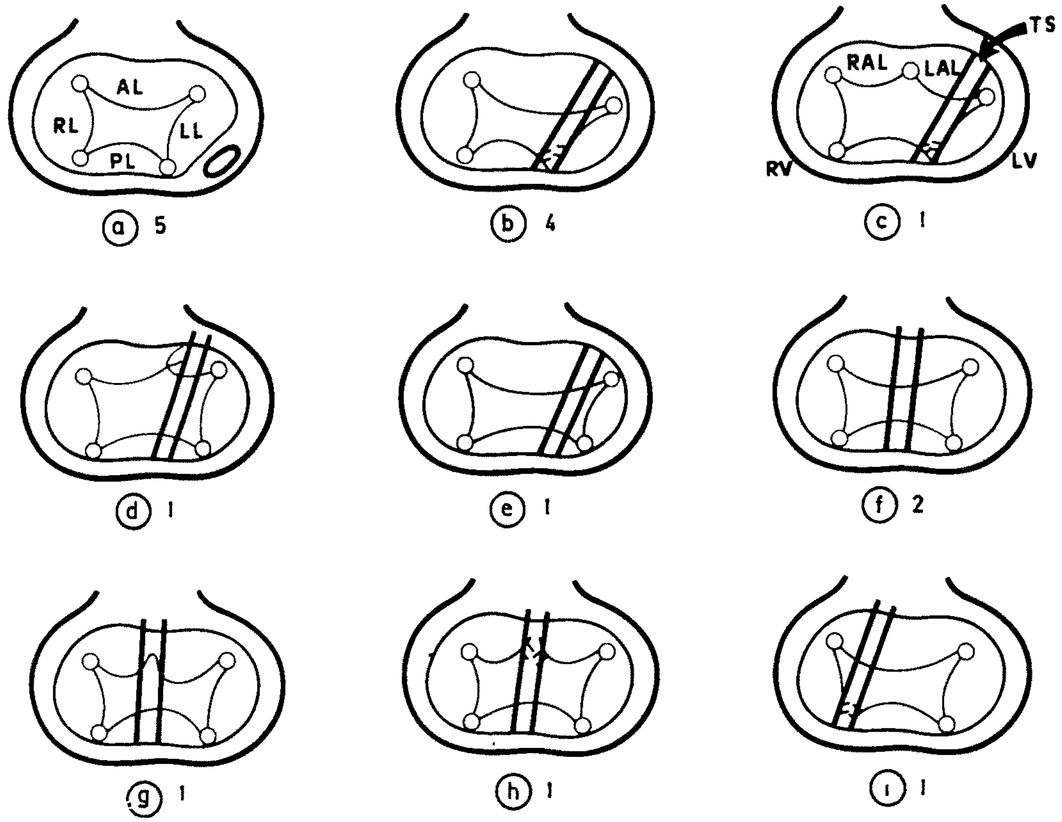


Fig 1 *Variation of the position of commissures detected by echocardiography. The leaflets of the common atrioventricular valve and the position of the commissures are shown in relation to the papillary muscles and trabecular ventricular septum in a short axis view. The right ventricle is on the left side. The number of patients is shown in parentheses. RV, right ventricle; LV, left ventricle; AL, anterosuperior leaflet; PL, posteroinferior leaflet; RL, right lateral leaflet; LL, left lateral leaflet; TS, trabecular septum; RAL, right anterosuperior leaflet; LAL, left anterosuperior leaflet.*

In two of four patients with a biventricular atrioventricular connection the anterosuperior leaflet was free floating and both the anterosuperior and posteroinferior leaflets straddled the interventricular septum (fig 1f). In another two patients two anterior leaflets were shown. One of them had no commissural cord between two anterosuperior leaflets (fig 1g, fig 4) and in the other the commissure between these leaflets was attached to the crest of interventricular septum (fig 1h, fig 5).

MORPHOLOGY OF LEAFLETS IN A PATIENT WITH LEFT VENTRICULAR DOMINANCE

The anterosuperior leaflet straddled the ventricular septum, and the commissure between right lateral and posteroinferior leaflets was attached to the ventricular septal crest (fig 1i, fig 6).

Discussion

A definite diagnosis of atrial isomerism can be made on the basis of the atrial morphology, especially the shape of the atrial appendage.[7] The morphology of the atrial appendage can be shown by atriography[8] or at operation. But atriography cannot be performed in all patients. There are only a few exceptions that show discordance between the thoracic situs and the atrial situs.[9] The most reliable non-invasive method of diagnosis is, therefore, to show the bronchial situs by a plain chest radiograph.[10-12] We detected bronchial isomerism by showing symmetrical main bronchi in a chest radiograph in our series. The course of the pulmonary arteries, which was shown by cineangiocardiography, was used to establish right or left sidedness.

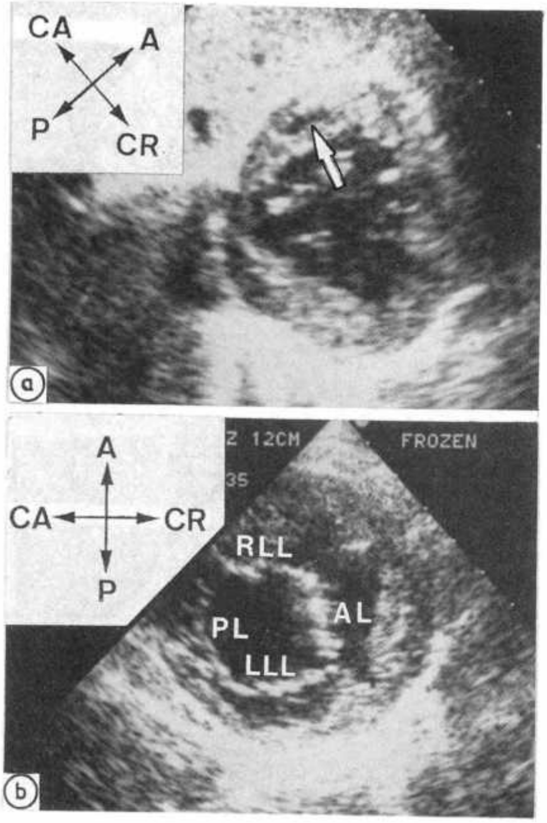


Fig 2 *Echocardiograms from a six year old boy with right isomerism (case 5) and left sided heart. (a) Subcostal short axis view showing a small rudimentary ventricle (arrow) positioned posteriorly with no chordal insertion into this ventricle. (b) Precordial short axis view showing four leaflets, all attached to the right ventricle.*
AL, anterosuperior leaflet; PL, posteroinferior leaflet; RLL, right lateral leaflet; LLL, left lateral leaflet; CR, cranial; CA, caudal; A, anterior; P, posterior.

Cross sectional echocardiographic identification of common atrioventricular valve in hearts with a double inlet ventricle is regarded as reliable.[5 13] We detected the cases of common atrioventricular valve by cross sectional echocardiography. Those with atresia of the left atrioventricular valve were also identified by cross sectional echocardiography and excluded from this study. Ventriculography was performed in all the patients and each of them had only one atrioventricular valve.

The common atrioventricular valve in hearts with the usual atrial arrangement and concordant atrioventricular connection was reported to have five leaflets—two anterosuperior, one posteroinferior, and right lateral and left lateral leaflets.[14] They were classified according to the position of attachment of commissural chordae of two anterosuperior leaflets.[14 15] Cross sectional echocardiography was reported to be the most effective method of detecting the detailed morphology of the common atrioventricular valve in terms of the description of the tethering position of the chordae of anterosuperior leaflets.[6] In our series, we identified four leaflets in nine of 10 hearts with a double inlet right ventricle or showing considerable right ventricular dominance. A necropsy study of hearts with double inlet right ventricle showed that the valve generally has four leaflets.[17] Four leaflets were also shown in three of six hearts with biventricular atrioventricular connec-

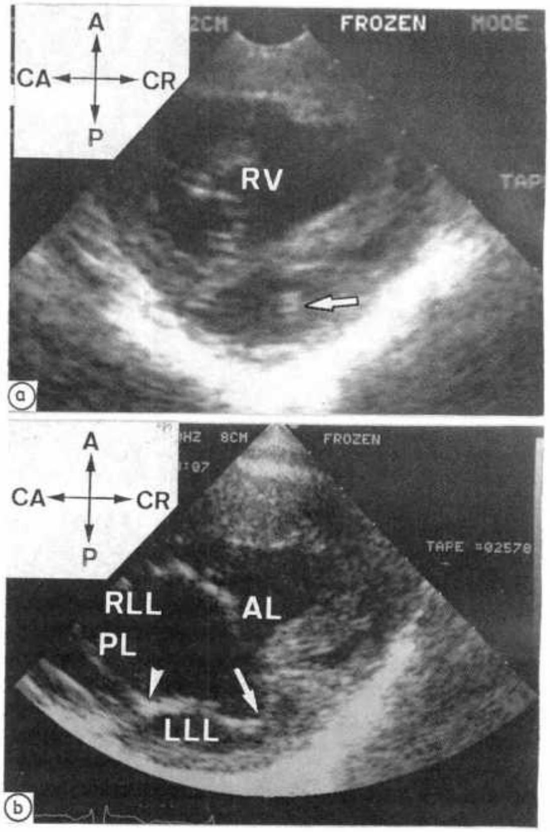


Fig 3 *Echocardiograms from a 11 year old boy (case 3) with left isomerism and a right sided heart. (a) Short axis view at papillary muscle level showing a dominant right ventricle (RV) and a papillary muscle (arrow) in the rudimentary left ventricle. (b) Short axis view at atrioventricular valve level showing the commissure (arrow) between the anterosuperior leaflet (AL) and left lateral leaflet (LLL) attached to the papillary muscle in the rudimentary left ventricle and the commissure (arrow head) between left lateral leaflet (LLL) and posteroinferior leaflet (PL) attached to the ventricular septal crest.*

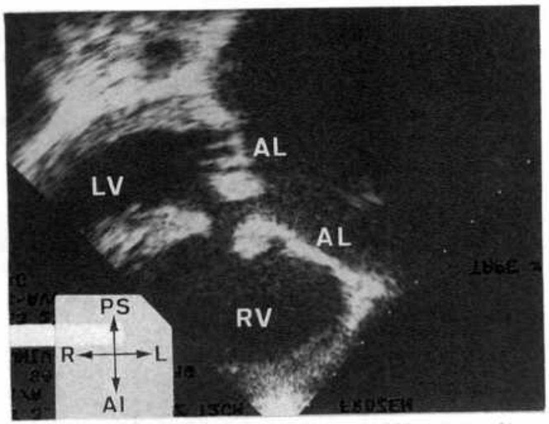


Fig 4 *Echocardiogram from a two year old boy (case 4) with left isomerism and a right sided heart. The four chamber view shows two well formed ventricles and a severely dilated atrium. The two anterosuperior leaflets (AL) were of equal size. There was no chordal tethering of the commissure between these two leaflets to the crest of ventricular septum or to a papillary muscle and the commissure was free floating. RV, right ventricle; LV, left ventricle; R, right; L, left; AI, anteroinferior; PS, posterosuperior.*

tion. It was impossible to detect another small right anterosuperior leaflet in the patients with a free floating large anterosuperior leaflet in the hearts of our series, as was shown in a necropsy study of common atrioventricular valve in hearts with the usual atrial arrangement and a concordant atrioventricular connection.[14]

In patients with two papillary muscles in the left ventricle and with slight right ventricular dominance or two well formed ventricles, the patterns of tethering of anterosuperior leaflets corresponded with those seen in patients with the usual atrial arrangement and a concordant atrioventricular connection—that is a free floating large anterosuperior leaflet, tethering of the commissure of two anterosuperior leaflets on to the medial papillary muscle, or tethering on to the crest of ventricular septum.

Left ventricular dominance was seen in only one patient, and in this patient the anterosuperior leaflet bridged the right ventricle while the commissural chordae of right lateral and posteroinferior leaflets were tethered on to the crest of the ventricular septum. In a necropsy study of patients with dominant left ventricles, only one commissural attachment to the right ventricle was shown and that was between the anterosuperior bridging leaflet and the anterolateral papillary muscle.[17]

The morphological characteristics of the common atrioventricular valve in atrial isomerism with right ventricular dominance or in hearts with double inlet right ventricle are not well known. In those patients with straddling of the mitral valve and two atrioventricular valves, the left ventricle generally had two papillary muscles, while the anterior papillary muscle was usually absent when there was one papillary muscle in the left ventricle.[18] On the other hand, in our series, the posterior papillary muscle was absent and the chordae of the commissure between the left lateral and posteroinferior leaflets were tethered to the crest of ventricular septum when one papillary muscle was found in the left ventricle. These differences suggest that the development of left ventricular hypoplasty differs in hearts with a straddling mitral valve and those with atrial isomerism and a common atrioventricular valve.

Hypoplasia and dysplasia of the left ventricular

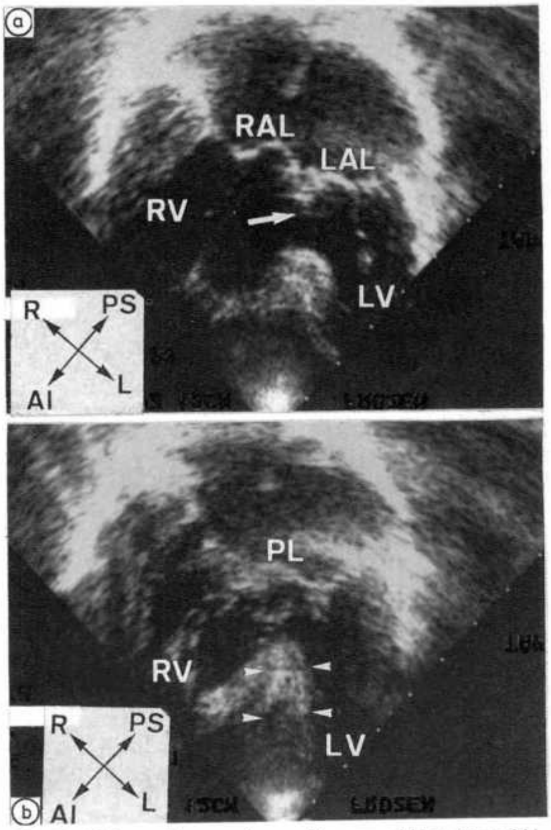


Fig 5 *Echocardiograms from a five year old boy (case 11) with right isomerism and a left sided heart. (a) The four chamber view shows two anterosuperior leaflets. Chordae (arrow) from the commissure of these leaflets were attached to the crest of the interventricular septum. RAL, right anterosuperior leaflet; LAL, left anterosuperior leaflet. (b) The four chamber view with posterior tilt shows a posteroinferior leaflet (arrow) that bridged the interventricular septum (arrow heads).*

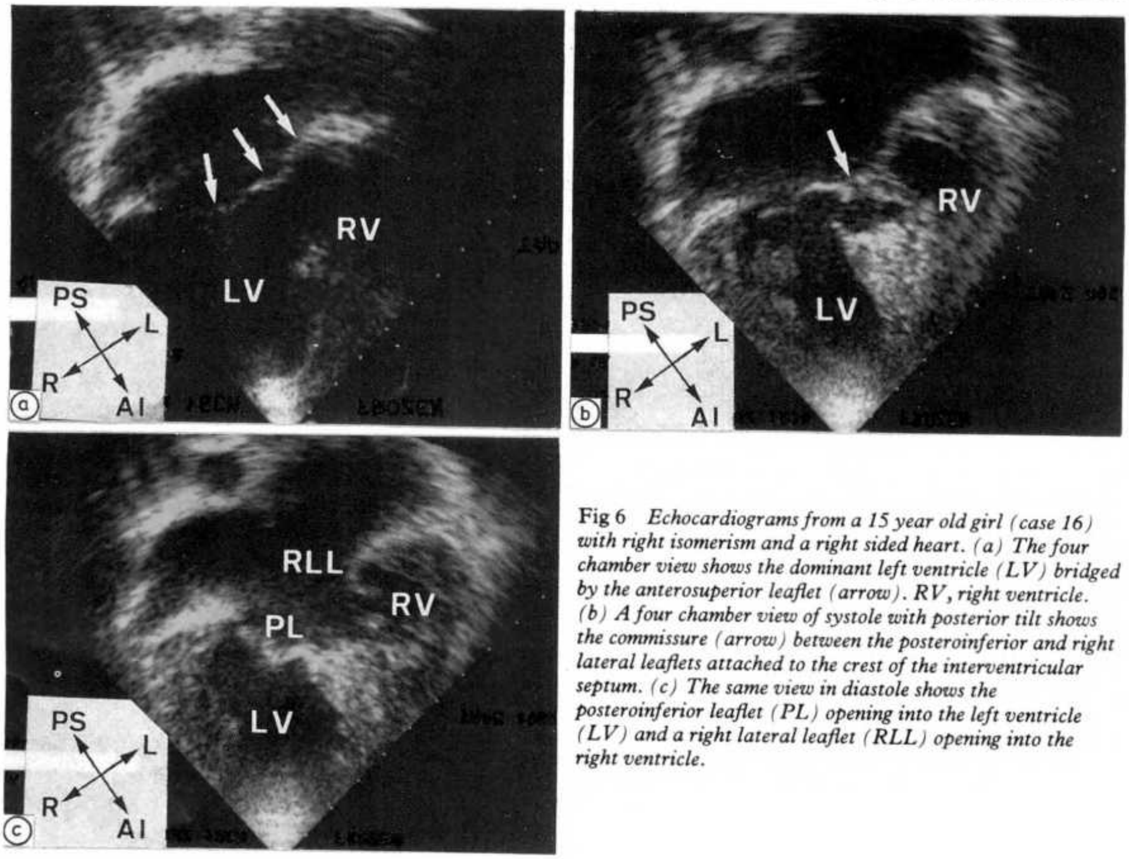


Fig 6 *Echocardiograms from a 15 year old girl (case 16) with right isomerism and a right sided heart. (a) The four chamber view shows the dominant left ventricle (LV) bridged by the anterosuperior leaflet (arrow). RV, right ventricle. (b) A four chamber view of systole with posterior tilt shows the commissure (arrow) between the posteroinferior and right lateral leaflets attached to the crest of the interventricular septum. (c) The same view in diastole shows the posteroinferior leaflet (PL) opening into the left ventricle (LV) and a right lateral leaflet (RLL) opening into the right ventricle.*

component of the posteroinferior leaflet and hypoplasia of the left ventricular posterior papillary muscle were reported in cases of common atrioventricular valve with the usual atrial arrangement, left ventricular hypoplasia, and normal relations of the great vessels.[19] The tethering of the commissure between the left lateral and posteroinferior leaflets to the crest of the ventricular septum that we found has not been described before in patients with the usual atrial arrangement.

Corrective surgery was performed in six patients. A total cavopulmonary shunt or modified Fontan procedure was performed in five patients with right ventricular dominance and in the patient with left ventricular dominance. Atrioventricular septation had been planned in one of the patients with right ventricular dominance, in whom the rudimentary left ventricle was large. The echocardiographic examination provided valuable information on which to base the surgical approach in this patient. Cross sectional echocardiography showed an atrioventricular valve of the type shown in fig 1b, and the modified Fontan procedure was performed.

We examined by echocardiography the range of types of common atrioventricular valve in atrial isomerism. We found that the atrioventricular morphology in those with partial insertion of a common atrioventricular valve into the rudimentary left ventricle in atrial isomerism differed from that in hearts with the usual atrial arrangement, concordant atrioventricular connection, and hypoplasia of the left ventricle.

References

1 Moller JH, Nakib A, Anderson RC, Edwards JE. Congenital cardiac disease associated with polysplenia. A developmental complex of bilateral "Left-Sidedness". *Circulation* 1967;**36**:789–99.

2 Liberthson RR, Hastreiter AR, Shinha SN, Bharati S, Novak GM, Lev M. Levocardia with visceral heterotaxy-isolated levocardia: pathologic anatomy and its clinical implications. *Am Heart J* 1973;**85**: 40–54.

3 Rose V, Izukawa T, Moës CAF. Syndromes of asplenia and polysplenia. A review of cardiac and non-cardiac

malformations in 60 cases with special reference to diagnosis and prognosis. *Br Heart J* 1975;37:840–52.

4 De Tommasi SM, Daliento L, Ho SY, Macartney FJ, Anderson RH. Analysis of atrioventricular junction, ventricular mass, and ventriculoarterial junction in 43 specimens with atrial isomerism. *Br Heart J* 1981;45: 236–47.

5 Smallhorn JF, Tommasini G, Macartney FJ. Two-dimensional echocardiographic assessment of common atrioventricular valves in univentricular hearts. *Br Heart J* 1981;46:30–4.

6 Smallhorn JF, Tommasini G, Anderson RH, Macartney FJ. Assessment of atrioventricular septal defects by two dimensional echocardiography. *Br Heart J* 1982;47:109–21.

7 Macartney FJ, Zuberbuhler JR, Anderson RH. Morphological considerations pertaining to recognition of atrial isomerism. Consequence for sequential chamber localisation. *Br Heart J* 1980;44:657–67.

8 Arciniegas JG, Soto B, Coghlan HC, Bargeron LM. Congenital heart malformations: sequential angiographic analysis. AJR 1981;137:673–81.

9 Caruso G, Becker AE. How to determine atrial situs? Considerations initiated by 3 cases of absent spleen with a discordant anatomy between bronchi and atria. *Br Heart J* 1979;41:559–67.

10 Van Mielop LHS, Eisen S, Schiebler GJ. The radiographic appearance of the trancheobronchial tree as an indicator of visceral situs. *Am J Cardiol* 1970; 26:432–5.

11 Deanfield JE, Leanage R, Stroobant J, Chrispin AR, Taylor JFN, Macartney FJ. Use of high kilovoltage filtered beam radiographs for detection of bronchial situs in infants and young children. *Br Heart J* 1980; 44:577–83.

12 Soto B, Pacifico AD, Souza AS Jr, Bargeron JM Jr, Ermocilla R, Tonkin IL. Identification of thoracic isomerism from the plain chest radiograph. *AJR* 1978;131:995–1002.

13 Rigby ML, Anderson RH, Gibson D, Jones ODH, Joseph MC, Shinebourne EA. Two dimensional echocardiographic categorisation of the univentricular heart. Ventricular morphology, type, and mode of atrioventricular connection. *Br Heart J* 1981; 46:603–12.

14 Piccoli GP, Wilkinson JL, Macartney FJ, Gerlis LM, Anderson RH. Morphology and classification of complete atrioventricular defects. *Br Heart J* 1979; 42:633–9.

15 Rastelli GC, Kirklin JW, Titus JL. Anatomic observations on complete form of persistent atrioventricular canal with special reference to atrioventricular valves. *Mayo Clin Proc* 1966;41:296–308.

16 Keeton BR, Macartney FJ, Hunter S, *et al.* Univentricular heart of right ventricular type with double or common inlet. *Circulation* 1979;59:403–11.

17 Bharati S, Lev M. The spectrum of common atrioventricular orifice (canal). *Am Heart J* 1973;86: 553–61.

18 Bharati S, McAllister HA, Lev M. Straddling and displaced atrioventricular orifices and valves. *Circulation* 1979;60:673–84.

19 Freedom RM, Bini M, Rowe RD. Endocardial cushion defect and significant hypoplasia of the left ventricle: a distinct clinical and pathological entity. *Eur J Cardiol* 1978;7:263–81.

Br Heart J 1989;62:298–304

Quantitative effects of speckle reduction on cross sectional echocardiographic images

R J MASSAY,* R B LOGAN-SINCLAIR,‡ J C BAMBER,† D G GIBSON*

*From the *Cardiac and ‡Bioengineering Departments, Brompton Hospital, London; and †Institute of Cancer Research, Sutton, Surrey*

SUMMARY Speckle is prominent on all cross sectional echocardiograms. In order to assess its effects on image quantification, frames from a sector scanner with a six bit grey scale were stored and processed off line to identify and smooth the speckle by means of an adaptive filter based on fully developed speckle. In 14 controls, 12 patients with hypertrophic cardiomyopathy, and 12 with secondary left ventricular hypertrophy, filtering significantly reduced the standard deviation of echo intensity, which was used as a measure of the scatter of pixel amplitude, in all three groups (by 52%, 46%, and 46% respectively). The mean value of back-scattered echo intensity itself, however, was reduced by only 7%, 5%, and 8% respectively, and median values were not affected at all. Mean (SD) left ventricular cavity areas on the apical four chamber view were significantly increased from 26 (15) to 30 (17) cm^2. The valve dimensions in the parasternal minor axis in 10 patients with mitral stenosis were significantly increased by 11% laterally, but were unaffected anteroposteriorly. Subjective image quality was appreciably modified: endocardial boundaries in apical views were enhanced and the septal "ground glass" appearance was lost in hypertrophic cardiomyopathy.

Speckle reduction therefore greatly reduced the scatter of pixel values, with little effect on the mean regional back scattered echo amplitude. It also modified the perceived image texture. Improved boundary definition consistently increased the area estimates, particularly when these depended on lateral rather than range resolution.

Speckle is present on all echocardiograms and gives them their characteristic granular appearance. Like noise it degrades the image, but unlike noise it is at least in part determinate—that is it is not random in its origin. Also, unlike electrical noise the global statistical properties of speckle, such as the grey scale histogram and spatial frequency spectrum, are predictable and specific to the imaging system being used.[1] These differences suggest it might be possible to identify and remove speckle from images by processing them.

We investigated such a system, based on adaptive filtering, and examined how it affected measurements often made on cross sectional echocardiograms: that is the local echo amplitude, the area enclosed by the ventricular cavity, and the dimensions of mitral valve orifice.

Patients and methods

Echocardiograms were recorded with an ATL 860 (6 bit) series scanner that was modified to increase its displayed dynamic range to 45 dB. On the final display, one grey scale level corresponded to 0·86 dB. Images were simultaneously displayed in grey scale and in colour by a Brompton encoder as they were recorded.[2] Gain settings were standardised: the master gain was increased until the pericardium posterior to the left ventricle was just displayed at the highest level on the encoder.[2] The depth compensation was then set to a linear ramp across the image at a rate of approximately 2 dB/cm. Gain settings were not altered thereafter. Standard echocardiographic cuts were used and images were stored on U-matic 3/4 inch video tape by a Sony VO 5800PS recorder.

Figure 1 shows the principle of the speckle reduction system we used.[1] It is based on the observation that an echocardiogram may show texture even when there is no resolvable or partially resolvable structure in the region being studied. Image texture of this sort

Requests for reprints to Dr D G Gibson, Brompton Hospital, Fulham Road, London SW3 6HP.

Accepted for publication 2 May 1989

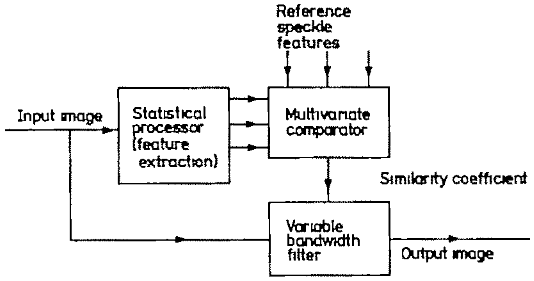

Reference speckle features
Input image
Statistical processor (feature extraction)
Multivariate comparator
Similarity coefficient
Variable bandwidth filter
Output image

Fig 1 *Principle of the adaptive filter used to reduce speckle.*

is referred to as fully developed speckle; its characteristics depend primarily on the imaging system used rather than on the target. Structure, resolvable or partially resolvable, only becomes apparent on the image when it modifies the background pattern of fully developed speckle. The system we used examined each small region of the image to determine how much its pattern of local pixel intensity resembled that of fully developed speckle. An index of similarity was thus derived, which controlled the spatial bandwidth of a smoothing filter. Regions of the image that most closely resemble fully developed speckle were heavily smoothed—that is replaced by the local mean—while regions that were least similar were not smoothed at all, leaving the original echo texture intact. We classified texture in terms of a variable, p, which represents the ratio of the local mean square pixel level to the local mean. The filtering process consists of modifying the original pixel intensity (x) to a new value ($\hat{x}$), given by:

$$\hat{x} = \bar{x} + k(x-\bar{x}),$$

where x represents the local mean, and k is given by the relation:

$$k = gp-\bar{p}s)/p,$$

where $\bar{p}s$ is the mean value of p in a region of fully developed speckle, and g is a scaling factor that determines the overall strength of the smoothing. The value of k has to be $\leqslant 1$, because if it is higher the edges become enhanced. Thus we computed the value for g for every tenth pixel matrix that gave a value of k just <1 over the whole image. Our algorithm differs slightly from that described by Bamber and Daft,[1] who used the ratio of local variance to local mean as the index of similarity, but found that it performed more satisfactorily for cardiological work where the data had undergone logarithmic compression and where the image contained large and small echo amplitudes close together.

The system was implemented on a Tandon PCA desk top computer. We derived the pixel distribution for fully developed speckle for our echocardiograph from a standard Nuclear Associates tissue-equivalent phantom at mid-depth. All scatterers within it, except for a set of wires, were assumed to be very small in comparison with the wavelength of ultrasound used. A matrix size of 5 × 5 pixels proved most satisfactory for processing, and values for g were usually in the range 1·3–1·5 depending on the image being studied. Video frames to be analysed were transferred from tape to a 512 × 256 × 6 bit frame store. We identified appropriate areas of interest, approximately 15 × 15 pixels; the local mean, median, and standard deviation were calculated for each and printed out, along with numbers of pixels at each of the 52 grey scale levels used. The frequency histogram was also displayed in analogue form on the image; this proved useful when we studied myocardial echoes because an obviously bimodal form usually meant that we had mistakenly included specular echoes (that is those reflected from large flat surfaces) within the area of interest. We could filter either the area of interest alone or the whole image; the whole image took approximately 70 s to complete when the matrix size was 5 × 5 pixels.

EFFECT OF SPECKLE REDUCTION ON A PHANTOM

Figure 2 shows the effect of speckle reduction on an image arising from a standard phantom. The unprocessed image (top panel) shows high amplitude echoes arising from wires embedded in it against a background of speckle. The middle panel shows the effect of the filter. The images of the wires are unaltered—indeed, their boundaries seem even more sharply defined than on the unprocessed image, but the speckle is much less prominent. The lowest panel is the result of subtracting the upper panel from the middle panel. Its amplitude has been doubled for clarity. It thus shows what has been removed from the original image by the filter. There is clearly no structural information at all here. Instead its texture is granular and virtually uniform. The unprocessed image can thus be thought of as combining this speckle pattern with the structural information shown in isolation in the middle panel.

EFFECT OF SPECKLE REDUCTION ON BACK-SCATTERED AMPLITUDE IN PATIENTS AND CONTROLS

The effect of reducing speckle on the amplitude of back-scattered echoes from myocardium was studied in 12 patients with typical hypertrophic cardiomyopathy (diagnosed on clinical and echocardiographic criteria), 12 with left ventricular hypertrophy secondary to valvar aortic stenosis severe enough to need valve replacement, and 14 normal controls. Areas of interest were located in the basal and mid-portions of the septum and posterior wall on the parasternal long axis cut,[3] excluding high amplitude

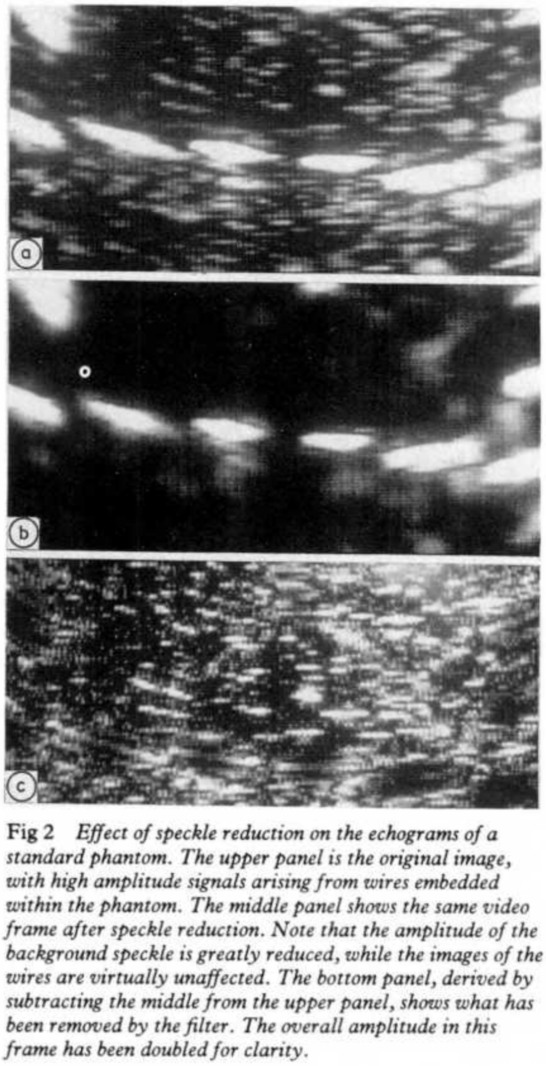


Fig 2 *Effect of speckle reduction on the echograms of a standard phantom. The upper panel is the original image, with high amplitude signals arising from wires embedded within the phantom. The middle panel shows the same video frame after speckle reduction. Note that the amplitude of the background speckle is greatly reduced, while the images of the wires are virtually unaffected. The bottom panel, derived by subtracting the middle from the upper panel, shows what has been removed by the filter. The overall amplitude in this frame has been doubled for clarity.*

echoes arising from endocardium or pericardium. We derived the mean pixel intensity and its standard deviation for each of these areas before and after applying the speckle reduction algorithm to the area of interest.

MEASUREMENT OF MITRAL VALVE DIMENSIONS AND LEFT VENTRICULAR CAVITY AREAS

We assessed how speckle reduction affected estimates of mitral valve dimensions from parasternal short axis cuts at the level of the valve cusps in 12 patients with rheumatic mitral stenosis. We photographed single frames on 35 mm film, along with the depth calibration before and after processing. With the image magnified 3–4 times, we measured the apparent dimensions of the valve orifice in the anteroposterior direction by the leading edge method and in the lateral direction from the "inside" of the cusp echoes.

We measured left ventricular cavity area on echocardiograms recorded in the apical four chamber cut in 11 patients with various cardiac conditions, including aortic regurgitation (two), rheumatic valve disease (three), cardiomyopathy (two), and four controls. Again we photographed the images on 35 mm film before and after processing and projected them on to a digitising table, outlining the area of the cavity as we have previously described for contrast angiograms.[5] On both processed and unprocessed images, we took the inner border of the echoes forming the cavity outline to be the position of the endocardium.

Results

BACK-SCATTERED AMPLITUDE

The table shows the values for the mean and standard deviation of back-scattered amplitude for controls and patients with primary and secondary left ventricular hypertrophy. Values from controls tended to be lower than those from patients with ventricular hypertrophy, but did not differ significantly. Similarly, mean values did not differ between patients with primary and secondary hypertrophy or between regions. Speckle reduction caused a very consistent reduction (46%–52%) in the standard deviations of pixel intensity in all three groups and values fell in every individual. The effect on the mean level of pixel intensity was very much smaller, ranging from a fall of 4·8% to a fall of 7·0%. These values were significantly less than the change in standard deviation ($p < 0{\cdot}001$ for all three groups).

Table *Effect of filtration on myocardial echo intensity*

	Unfiltered values			*Change with filtration (%)*		
Group	*Mean*	*SD*	*Median*	*Mean*	*SD*	*Median*
Control	7·3	4·4	6·3	−7·0	−52	−0·7
Hypertrophic cardiomyopathy	8·2	4·2	7·7	−5·9	−46	−2·3
Secondary left ventricular hypertrophy	9·0	4·4	7·7	−4·8	−46	−1·5

All the differences between the percentage change in standard deviation for median or mean values were significant ($p < 0{\cdot}001$).

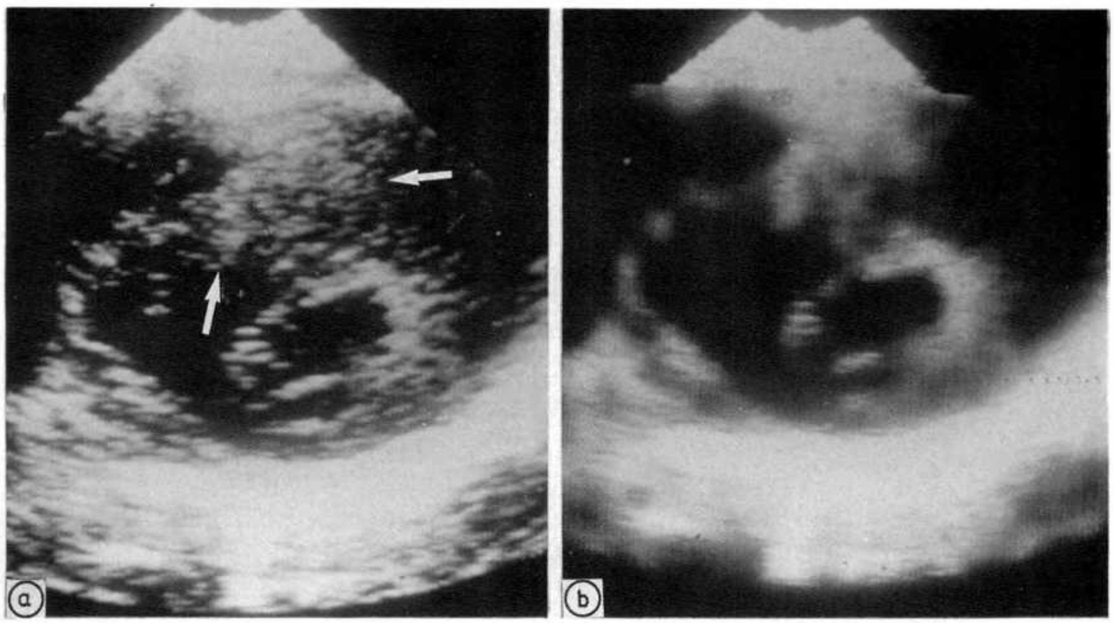


Fig 3 *Effect of speckle reduction on myocardial echo texture in a patient with hypertrophic cardiomyopathy (parasternal minor axis cut). Note that the granular appearance of the myocardium in the original image (left, arrows) has been removed by processing, and replaced by a more diffuse structure.*

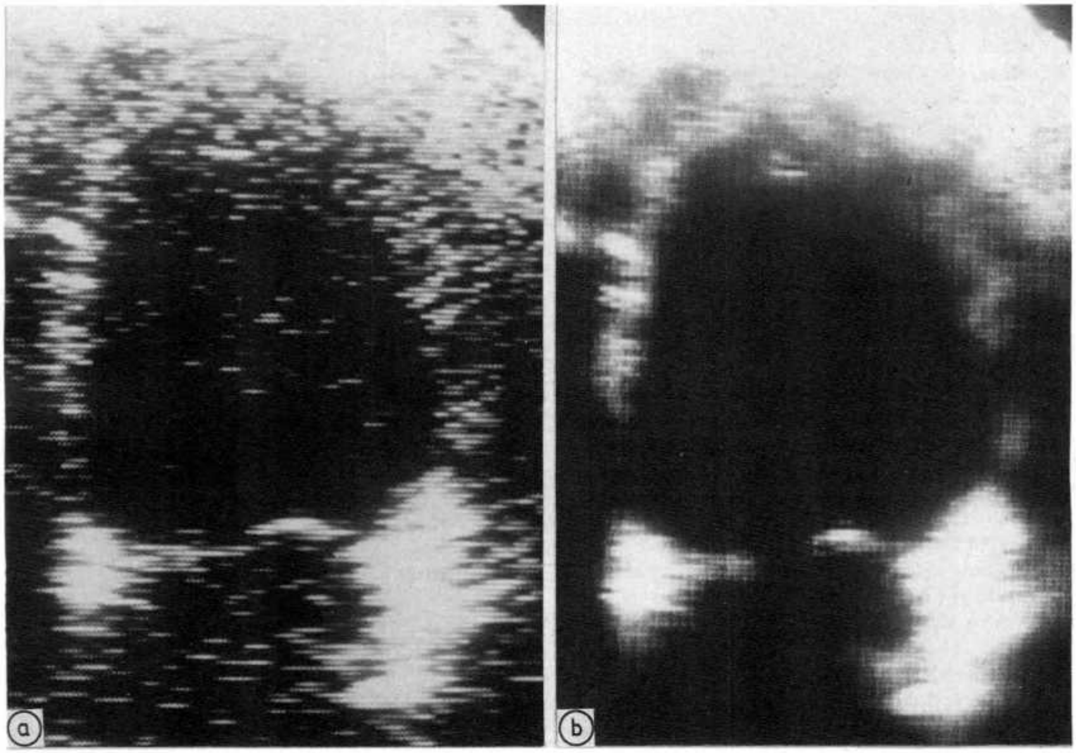


Fig 4 *Left ventricular echocardiogram (apical four chamber cut) showing the effect of speckle reduction on the apparent cavity size and endocardial boundary. Left, original image; right, filtered image.*

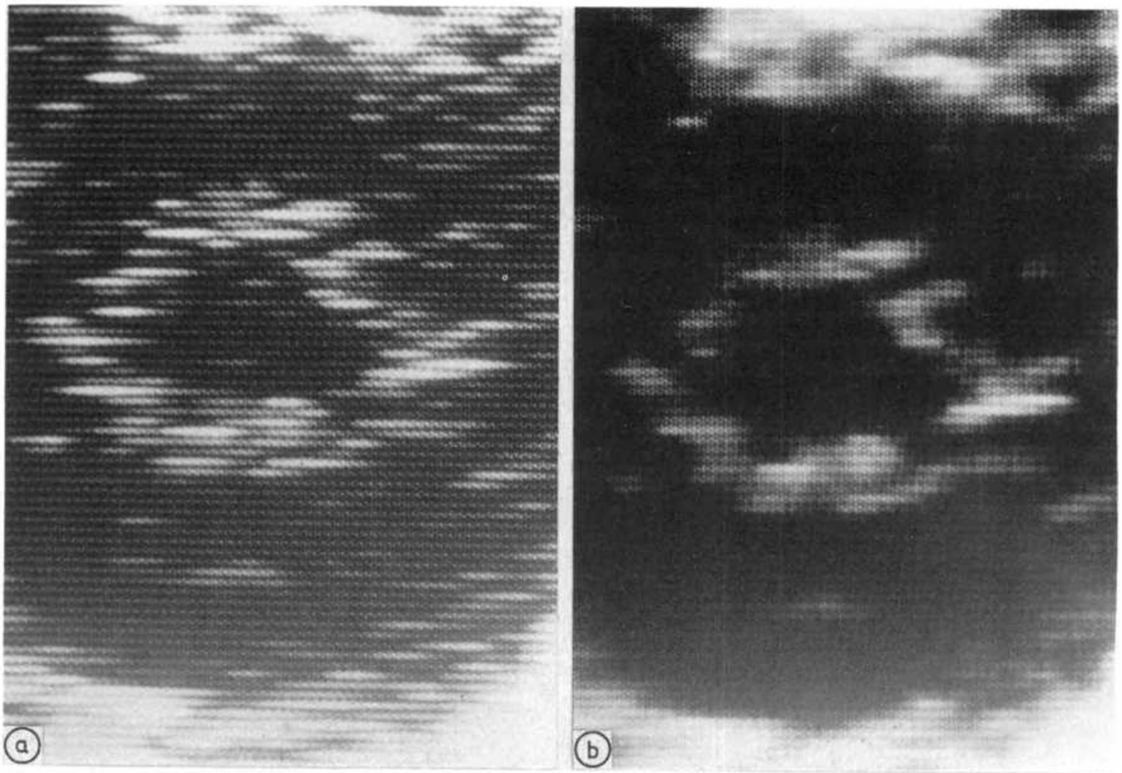


Fig 5 *Mitral valve orifice, recorded in parasternal minor axis cut from a patient with mitral stenosis. Left, original image; right, processed image. Note that the apparent orifice size has increased and that its boundary appears more clearly defined.*

The median pixel level did not show any consistent change.

Reducing speckle caused the images to change strikingly. In the patients with left ventricular hypertrophy, whether primary or secondary, echo texture often seemed abnormal before processing, with an obvious granular appearance (fig 3, left panel). After speckle reduction, this granularity was no longer present (right panel) and was consistently replaced by a diffuse pattern of echoes within the myocardium. Apparently randomly distributed, sharply defined sonolucent areas were strikingly accentuated; although in retrospect they had been present on the unprocessed image, they became much more obvious once the speckle had been reduced. Their origin was not clear though their consistent presence and position on successive frames seem to suggest that they were not artefactual.

LEFT VENTRICULAR CAVITY AREA

The apparent left ventricular cavity area was consistently larger after speckle reduction (fig 4). The mean value rose from 26 (15) cm^2 to 30 (17) cm^2 on the processed image ($p < 0{\cdot}002$), the increase being at least 1 cm^2 in each patient. Subjectively, we noted that the internal boundary of the cavity became much clearer, making it easier to digitise (fig 4).

ORIFICE DIMENSIONS OF THE MITRAL VALVE

On the parasternal minor axis view, mitral valve dimensions in the anteroposterior direction were unaffected by speckle reduction, the mean (SD) being unchanged at 21 (12) mm. The transverse dimension, however, increased from 36 (9) mm on the unprocessed image to (40) (12) after filtering (fig 5) ($p < 0{\cdot}002$). Again, the apparent boundary of the orifice became much clearer after the image had been processed.

Discussion

Speckle is prominent in all ultrasound images. It is probably caused when wave fronts from targets that are too small to be individually resolved at the wavelength of ultrasound used interfere with one another. The exact pattern seems to depend mainly on the echocardiograph used, and it is still not certain whether it conveys any structural information at all.

The overall result of speckle, however, is to degrade fine detail, so it was of interest to examine how cardiological images were altered when it was substantially reduced.

There are several ways in which this might have been done. Speckle can be treated simply as noise and reduced by frame averaging or smoothing. While this would certainly reduce its overall effect, spatial and temporal information would also be lost. A second approach would be to use more than one transducer —again this might have been possible with a static organ, but it would be quite impracticable for the heart without losing diagnostically valuable information. Our approach identified the speckle pattern characteristic of the echocardiograph we used, determined its statistical features, and smoothed it on the image. This approach proved feasible, and it may well be possible to implement it in real time. The median pixel level did not change, and the mean pixel level fell very slightly. The scatter of pixel levels around these mean values, however, was strikingly reduced. Using the phantom, we showed that our ability to detect high frequency detail was unaffected. Further, had there been any non-specific smoothing, we would have found it on the subtraction image where it would have appeared as high frequency boundaries to the structural features. Altogether, the way regional amplitude and local pixel distribution changed was quite compatible with speckle reduction, and cannot be explained by simple smoothing of the image.

It seems to be generally accepted that echocardiograms are granular, and thus qualitatively different from the images produced by other methods such as computed tomography or magnetic resonance imaging. Does a granular texture reflect anything fundamental about myocardium? There is some clinical evidence to suggest that it might. A "ground glass appearance" of the septum is said to be characteristic and even diagnostic of hypertrophic cardiomyopathy.[4] Myocardial texture has been analysed on the basis of the presence, distribution, and size of what are described as "highly refractile bodies".[6] The myocardium is unusual among the cardiac structures commonly studied by echocardiography, in being detected almost entirely from back-scattered echoes rather than from specular reflection, as are the valves and endocardial surfaces. These back-scattered echoes arise from targets that are small compared with the wavelength of ultrasound used, and so the resulting image is likely to be more sensitive to the effects of speckle than one based mainly on specular echoes. Not surprisingly, therefore, the effect of reducing speckle by a system based on single feature criteria on myocardial texture was profound. It no longer appeared granular, even in patients with hypertrophic cardiomyopathy or secondary left ventricular hypertrophy, implying that the apparent texture in the unprocessed images had corresponded very closely with the criteria we used to identify fully developed speckle. By contrast, median pixel levels, which are not affected by speckle, were unaltered. We conclude that the granular appearance within the myocardium in these patients need not reflect underlying structure in any significant way. We did not establish whether the appearances shown by filtering had any anatomical basis. This will require further study.

Areas are often measured routinely on cross sectional images so we studied two examples. In patients with rheumatic mitral stenosis the anterioposterior dimension of the valve orifice was unaffected by filtering the image but the lateral dimension was consistently larger, so that the calculated area increased. The apparent left ventricular cavity area as assessed in the apical four chamber view was approximately 15% larger when measured on processed images. This increased to 25% when the volume was estimated. These differences are large enough to be clinically significant. The effect of processing on the apparent area seemed to be related to the way in which the image of the corresponding boundary was generated. On the short axis parasternal cut that is traditionally used to measure mitral valve area a leading edge defines the apparent orifice only along the anterior surface of the posterior cusp. The trailing edge of the anterior cusp forms its anterior border, while the commissures are defined by lateral resolution. Thus both they and the ventricular cavity on the apical four chamber view are outlined by back-scattered rather than reflected echoes and so they are likely to be particularly sensitive to the effects of superimposed speckle. It follows that even a measurement so seemingly unambiguous as the area enclosed by what appear to be clear anatomical boundaries on an echocardiogram depends critically on how the image is generated.

Smoothing,[7] frame averaging,[8] boundary enhancement,[9 10] and colour coding[2] have been examined for their possible value in processing echocardiograms. All these manoeuvres have in common a non-specific algorithm, so their value is limited to accentuating information already present on the unprocessed image. More complex analysis requires that the processes underlying image generation be better understood, so that confounding factors can be identified and removed. Speckle reduction seems to be a step in this direction, though the physics of its production do not have to be understood in detail for its effects to be quantified and isolated. We hope to improve these methods so that they can be used in real time, rather than simply on individual frames. Ideally, echocardiographs would be designed to eliminate speckle as the original data are collected rather than to remove it retrospectively from the final image as we have done. As the interaction between ultrasound and tissues becomes more clearly understood, we expect that equipment design will improve so that the resolution and information content of images will correspondingly increase.

References

1 Bamber JC, Daft C. Adaptive filtering for reduction of speckle in ultrasonic pulse-echo images. *Ultrasonics* 1986;5:41–4.

2 Logan-Sinclair R, Wong CM, Gibson DG. Clinical application of amplitude processing of echocardiographic images. *Br Heart J* 1981;45:621–7.

3 Edwards WD, Tajik AJ, Seward JB. Standardized nomenclature and anatomic basis for regional tomographic analysis of the heart. *Mayo Clin Proc* 1981; 56:479–97.

4 Martin RP, Rakowski H, French J, Popp RL. Idiopathic hypertrophic subaortic stenosis viewed by wide-angle phased array echocardiography. *Circulation* 1979;**59**:1206–17.

5 Gibson DG, Prewitt TA, Brown DJ. Analysis of left ventricular wall movement during isovolumic relaxation and its relation to coronary artery disease. *Br Heart J* 1976;**38**:1010–9.

6 Bhandari AK, Nanda NC. Myocardial texture characterization by two-dimensional echocardiography. *Am J Cardiol* 1983;**51**:817–25.

7 Parker DL, Pryor TA, Ridges JD. Enhancement of two-dimensional echocardiographic images by lateral filtering. *Comp Biomed Res* 1979;**12**:265–77.

8 van Ocken E, Claes V, Brutsaert DL. Image enhancement by digital averaging of 2-dimensional echopictures. In: Latin V, ed. *Proceedings: Fourth European Congress on Ultrasound in Medicine*. Amsterdam: Excerpta Medica, 1981:69.

9 Grube E, Becher H, Backs B. Automatic contour finding and digital subtraction technique in 2-dimensional echocardiography. In: Roelandt J, ed. *Digital techniques in echocardiography*. Dordrecht: Martinus Nijhoff, 1987:99–122.

10 Skorton DJ, McNary CA, Child JS, Newton FC, Shah PM. Digital image processing of two dimensional echocardiograms; identification of the endocardium. *Am J Cardiol* 1981;**48**:479–86.

Br Heart J 1989;62:305–10

Magnetic resonance imaging at a high field strength of ventricular septal defects in infants

E J BAKER, VICTORIA AYTON,* M A SMITH,* J M PARSONS, E J LADUSANS, R H ANDERSON,† M N MAISEY,* M TYNAN, NUALA L K FAGG,‡ P B DEVERALL§

*From the Departments of Paediatric Cardiology, *Radiological Sciences; §Cardiothoracic Surgery; and ‡Histopathology, Guy's Hospital; and †Cardiothoracic Institute, London*

SUMMARY Magnetic resonance imaging at a high field strength has potential benefits for the study of the heart in infants, which is when most congenital heart disease presents. Seventeen infants with various anatomical types of ventricular septal defect were studied by this technique. Good quality, high resolution, images were obtained in every case. There were no major practical problems. The morphology of the defects in all 17 hearts was displayed in great detail. In some instances, the interpretation of the images resembled that of equivalent images from cross sectional echocardiography. But this new technique allowed imaging in planes that cannot be obtained by echocardiography. One particularly valuable plane gave a face on view of the inlet and trabecular components of the septum. This allowed very precise localisation of defects in these areas. The relation between the defects and the atrioventricular and arterial valves was exceptionally well shown in various different imaging planes. One patient in the series had multiple trabecular defects that were clearly shown.

Magnetic resonance imaging gives detailed morphological information about ventricular septal defects.

High resolution cross sectional imaging can provide a precise description of the morphology of defects in the ventricular septum,[1] and echocardiography is a useful investigation in patients with such defects. But newer cross sectional imaging methods have not been evaluated in the study of ventricular septal defects. Gated cardiac magnetic resonance imaging, with imaging systems of low field strength, can detect large defects in older patients.[2 3] The structural diagnosis of congenital heart defects, however, is usually made in infants.[4] This is the age group in which new imaging techniques need to be evaluated.

We studied an unselected series of infants with various types of ventricular septal defect by a magnetic resonance imaging system that operates at high field strength.

Patients and methods

PATIENTS

We studied 17 infants with ventricular septal defects undergoing clinical assessment at Guy's Hospital (table). The selection criteria were the presence of a known ventricular septal defect and the availability of the infant for imaging. They were aged between three weeks and six months. All had a normal atrial arrangement. Nine had normal cardiac connections. In three there was a discordant ventriculoarterial connection, and one of these infants also had a discordant atrioventricular connection. Two cases had double outlet from the morphologically right ventricle, two others had pulmonary atresia, while the final patient had a common arterial trunk. One patient has since died and the heart has been examined (patient 5). Another has undergone surgical closure of the defect (patient 17).

METHODS

The imaging protocol was described in detail elsewhere.[5] In all patients an initial series of sections was acquired in the transverse plane of the body, encompassing the whole heart. Typically, this required seven sections. Subsequent imaging planes were chosen in the light of the suspected cardiac abnormality and the position and orientation of the cardiac structures as shown on these images. Imaging planes

Requests for reprints to Dr E J Baker, Department of Paediatric Cardiology, Guy's Hospital, London SE1 9RT.

Accepted for publication 10 May 1989

Table *Details of patients studied by magnetic resonance imaging at high field strength*

Case No	*Age*	*Morphology demonstrated by magnetic resonance*
1	3 mnth	Large muscular inlet defect, multiple small muscular trabecular defects
2	4 mnth	Double outlet of the morphologically right ventricle, anterior aorta, posterior pulmonary trunk overriding a perimembranous confluent defect
3	3 wk	Pulmonary atresia, aorta arising anteriorly from the right ventricle, no central pulmonary arteries, muscular outlet defect
4	4 mnth	Perimembranous confluent defect with overriding by the tricuspid valve and malalignment between the atrial septum and the trabecular ventricular septum
5	3 mnth	Double outlet of the right ventricle with the great arteries arising, side by side, the aorta to the right, complete muscular infundibulum beneath both great arteries, defect with entirely muscular margins
6	6 wk	Doubly committed juxta-arterial defect with muscular posteroinferior border, coarctation
7	4 mnth	Pulmonary atresia with central confluent pulmonary arteries; aortic valve overrides a perimembranous outlet defect
8	6 wk	Perimembranous inlet defect with accessory tricuspid valve tissue partially closing it
9	3 mth	Small perimembranous defect with accessory tricuspid valve tissue
10	1 mnth	Muscular outlet defect, complete muscular subaortic infundibulum coarctation
11	5 mnth	Discordant ventriculoarterial connection, muscular outlet defect with posterior deviation of the outlet septum and subpulmonary stenosis
12	1 mnth	Perimembranous confluent defect with overriding tricuspid valve, overriding aortic valve, and infundibular pulmonary stenosis
13	3 wk	Perimembranous defect with overriding common arterial trunk
14	2 mnth	Small perimembranous defect, coarctation
15	5 mnth	Discordant ventriculoarterial connection, muscular outlet defect
16	1 mnth	Discordant atrioventricular and ventriculoarterial connections; perimembranous outlet defect with overriding pulmonary valve
17	6 mnth	Single large muscular inlet defect

oblique in one or two axes to the standard planes of the body were used in every patient. The angles for these planes were measured individually in each patient from the earlier images. Optimum imaging of the cardiac anomaly was achieved typically in total imaging time of about 90 minutes.

Results

Images of adequate quality for morphological study were obtained in every patient. The electrocardiographic gating was also satisfactory in all instances.

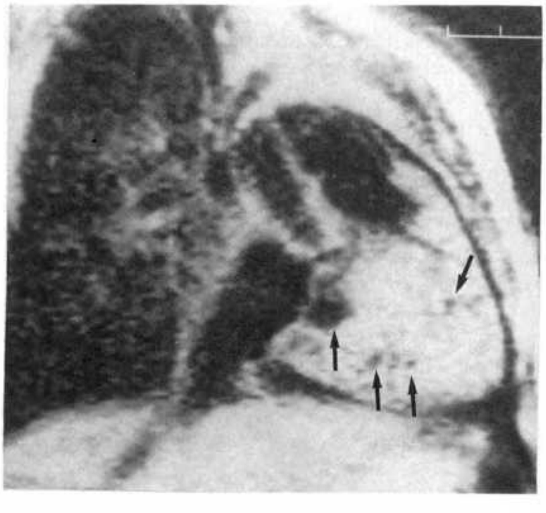


Fig 1 *Magnetic resonance image of oblique coronal section in patient 1. The section includes the ventricular septum and shows multiple muscular defects (arrows), the largest being in the inlet septum. There is no defect in the outlet septum; it appears to be defective because it curves backwards out of the plane of the section.*

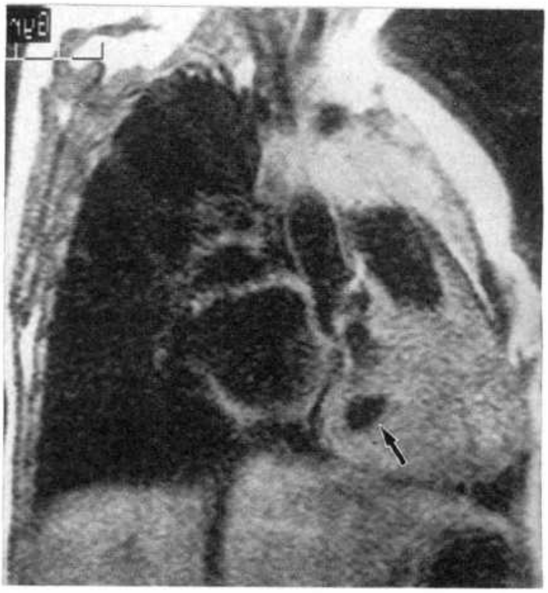


Fig 2 *Magnetic resonance image of oblique coronal section in patient 17. There is a single large muscular defect (arrow). The membranous septum was shown to be intact in sections orthogonal to this; because it is thin it appears to be defective in this plane.*

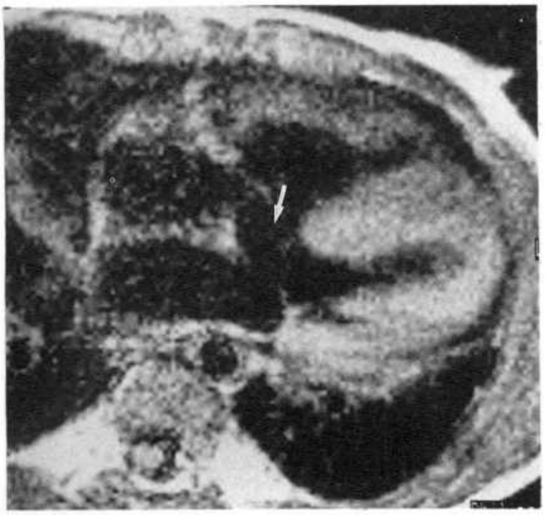


Fig 3 *Magnetic resonance image of oblique transverse, four chamber cut, in patient 2 showing that the defect between the ventricular inlets is perimembranous (arrow). The defect is "roofed" by the area of fibrous continuity between the atrioventricular valves, which are not offset.*

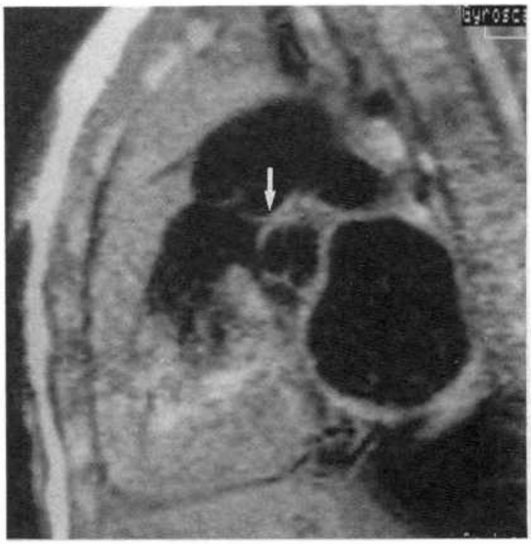
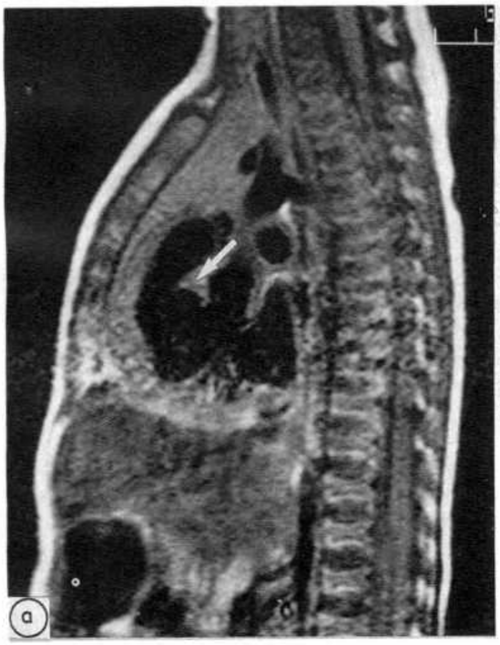


Fig 5 *Magnetic resonance image of oblique sagittal cut to show the septum in patient 6 who had a doubly committed juxta-arterial defect. The area of fibrous continuity between the arterial valves is clearly shown (arrow). There is some offsetting between the pulmonary and aortic valves in this section.*

The table lists the descriptions of the morphology that were discernible from the magnetic resonance images. The morphological criteria for the description of ventricular septal defects have been described in detail elsewhere.[1] In the two patients in whom direct observation of the morphology of the defect was possible at necropsy or operation the magnetic resonance description of the defects was confirmed.

Although the imaging planes used in each patient were different, some general principles emerged. For



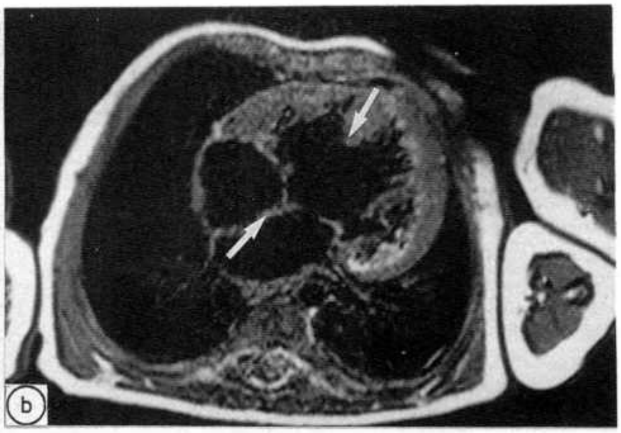


Fig 4 *(a) Magnetic resonance images of a sagittal cut of a confluent perimembranous defect (patient 4). This shows the outlet extension of the defect, with the outlet septum clearly delineated (arrow). (b) Oblique transverse, four chamber, cut in the same patient. There is a large perimembranous defect between the ventricular inlets with malalignment between the atrial septum and ventricular septum (arrows).*

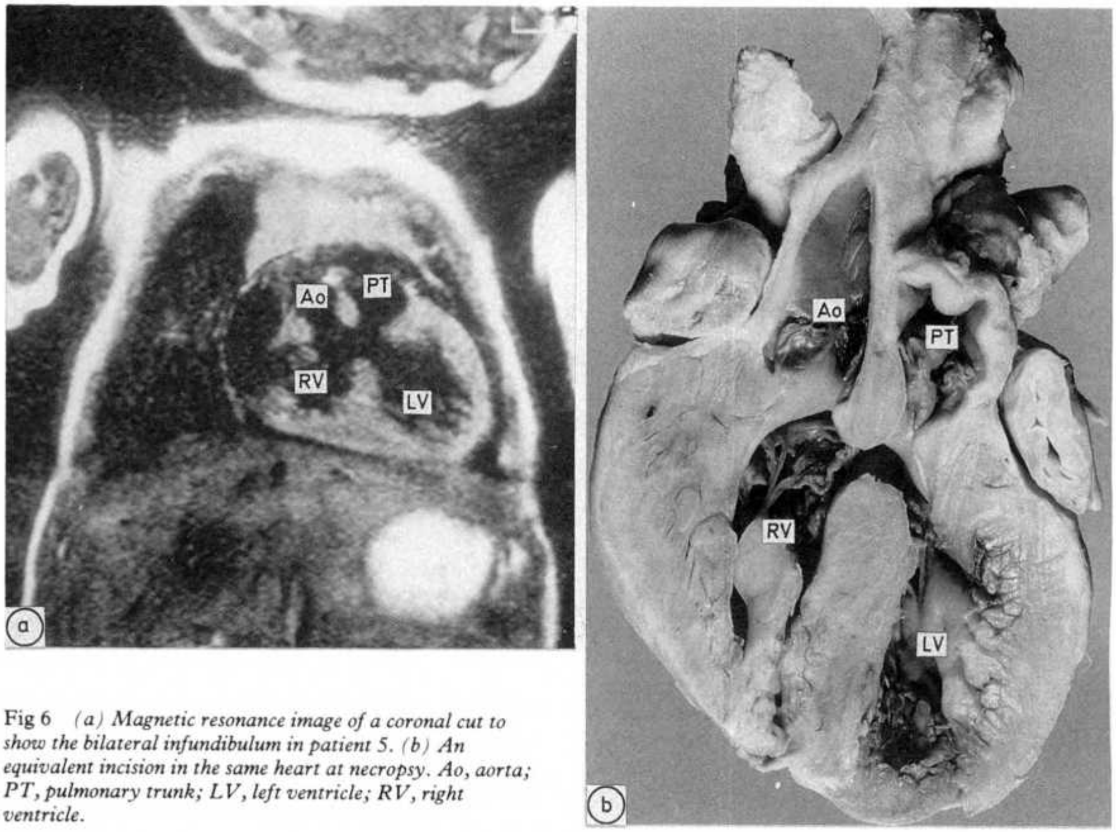


Fig 6 *(a) Magnetic resonance image of a coronal cut to show the bilateral infundibulum in patient 5. (b) An equivalent incision in the same heart at necropsy. Ao, aorta; PT, pulmonary trunk; LV, left ventricle; RV, right ventricle.*

instance, the oblique coronal plane was a particularly valuable imaging plane (rotated around a vertical axis, and also occasionally a left to right axis, in the plane of the inlet and trabecular components of the ventricular septum). This included a large part of the septum within the 5 mm thick slice. This imaging plane clearly showed the position of defects in the inlet and trabecular septum and their relation to the central fibrous body. This section needed careful selection of the imaging plane and was not satisfactorily achieved in every patient. In patient 1, such a section clearly showed not only a large muscular inlet defect, but also several small muscular trabecular defects (fig 1). In contrast, in patient 17 a similar image showed a single large defect with entirely muscular margins in the inlet septum (fig 2). An oblique sagittal plane rotated around both the vertical and anterioposterior axes was used to show the ventricles in short axis. A four chamber image, showing the inlet septum, was obtained from an oblique transverse plane, rotated around the left to right and anterioposterior axes (fig 3). Frequently, even with large defects, the morphology could not be clearly determined from standard imaging planes. The use of oblique imaging planes individually tailored to the morphology seen in each case was essential (figs 4, 5, and 6). The morphology of the ventricular septal defects studied in this series was very varied. There was no standard imaging protocol that would have provided the best images in every patient.

Discussion

This series contains examples of a wide variety of anatomical types of ventricular septal defects. In every patient, the magnetic resonance study provided the morphological details to define the anatomy of the defects present. The high resolution of the images obtained, even in these small infants, compares favourably with those from cross sectional echocardiography. A unique feature of magnetic resonance imaging is its capability to image in any plane through the heart. There should in theory, therefore, be no feature of the morphology of any ventricular septal defect that cannot be determined within the limits of resolution of the images. Further experience will indicate whether this is indeed true. It is already clear to us that considerable experience is required in choosing the best imaging plane in individual patients. We believe that the standard series of imaging planes that have been described by others,[6] have no place in the imaging of congenital malformations of the heart. The protocol in each patient has to be matched to the observed anatomy. This is already well established in echocardiography. The same general principles about the interpretation of cross sectional images of the heart apply to magnetic resonance images.

POSITION OF THE DEFECT IN THE VENTRICULAR SEPTUM

Magnetic resonance images in planes that are equivalent to cross sectional echocardiographic imaging planes can be interpreted by the same criteria.[1] Thus the defect can be judged as solely opening between the ventricular inlets, solely between the subarterial outlets, or extending between these areas, when they may be termed "confluent" (fig 5). Although there are no examples in this series, large isolated muscular trabecular defects should be demonstrable in such planes. In addition, we showed a new approach to imaging the ventricular septum that is exclusive to the technique of magnetic resonance imaging. Sections in the plane of, and enclosing, the inlet and trabecular components of the septum produce images comparable to seeing these areas of the septum directly. Defects in these areas can then be precisely localised.

RELATION OF THE DEFECT TO ARTERIAL VALVES

Examples of muscular, perimembranous, and doubly committed juxta-arterial defects all opening between the subarterial outlets are included in this series. The outlet septum cannot be shown face on in the same way as the inlet and trabecular components of the septum. This is because, in hearts with normal connections, the septum curves posteriorly out of the imaging plane. Despite this, extension of defects to open between the subarterial outlets was exceptionally well shown. For example, the fibrous continuity between aortic and pulmonary valve in a patient with a doubly committed defect was very clear (fig 5). A comparison of the necropsy specimen with the magnetic resonance images in a patient with a bilateral infundibulum shows how well this aspect of the anatomy was shown (fig 6). Features such as overriding of arterial valves and deviation of the outlet septum were also well shown.

RELATION OF THE DEFECT TO THE CENTRAL FIBROUS BODY AND ATRIOVENTRICULAR VALVES

The relation of defects to the central fibrous body was shown in various planes. So perimembranous defects were readily distinguished from other defects. Perimembranous defects extending into the inlet septum and roofed by the atrioventricular valves were well shown in a four chamber imaging plane. In two patients in this series such defects were associated with overriding of the tricuspid valve. This was clearly shown (fig 4). In one of these, however, there was echocardiographic evidence of additional straddling of the tension apparatus of the valve that was not evident on the magnetic resonance images.

MULTIPLE DEFECTS

In one patient in this series, the magnetic resonance images clearly showed multiple small trabecular defects in association with a large muscular defect of the inlet septum (fig 1). Only one trabecular defect was shown in this patient on both Doppler colour flow mapping and cineangiography. It is, therefore, possible that magnetic resonance imaging will prove of special value in detecting the presence of multiple defects. Great care is needed to differentiate trabeculations on the right ventricular surface of the septum from true small trabecular defects. By following the defects in contiguous sections from the cavity of the left ventricle to that of the right we were confident that in this patient they were true septal defects. If this is not always done, trabeculations will be falsely identified as septal defects.

THE PLACE OF MAGNETIC RESONANCE IMAGING

There are few practical problems with this imaging technique. The patient must be prevented from moving. We found that light sedation was sufficient for this. The infant does not suffer any discomfort during the imaging procedure and, if well prepared, will generally sleep soundly. The heart rate is constantly monitored and the patient's colour and respiratory motion can be observed from outside the magnet. Cardiac gating was a potential problem because of possible distortion of the electrocardiogram. But we have not found any major difficulty with this. Occasionally the position of the electrodes has to be adjusted to give the best signal, but we have always been able to obtain satisfactorily gating.

Magnetic resonance imaging can, therefore, provide excellent images of ventricular septal defects. Much of the information they contain is comparable with that from cross sectional echocardiography. The images, however, are of high resolution, and new imaging planes that are not possible with echocardiography can be used. This new technique enables a very detailed assessment of the morphology of ventricular septal defects to be made non-invasively. This calls into question the role of cineangiography in the assessment of infants with ventricular septum defects.

This research was supported by the British Heart Foundation. The imaging system was purchased with the assistance of Sir Philip and Lady Harris and the Special Trustees of Guy's Hospital.

References

1 Baker EJ, Leung MP, Anderson RH, Fischer DR, Zuberbuhler JR. The cross sectional anatomy of ventricular septal defects: a reappraisal. *Br Heart J* 1988;**59**:339–51.

2 Didier D, Higgins CB, Fischer MR, Osaki L, Silverman NH, Cheitlin MD. Congenital heart disease: gated MR imaging in 72 patients. *Radiology* 1986;**158**: 227–35.

3 Underwood SR, Firmin DN, Klipstein RH, Rees RSO, Longmore DB. Magnetic resonance velocity mapping: clinical application of a new technique. *Br Heart J* 1987;**57**:404–12.

4 Hoffman JIE, Christianson R. Congenital heart disease in a cohort of 19,502 births with long term follow up. *Am J Cardiol* 1978;**42**:641–7.

5 Baker EJ, Ayton V, Smith MA, *et al.* Magnetic resonance imaging of coarctation of the aorta in infants: use of a high field strength. *Br Heart J* 1989;**62**:97–101.

6 Didier D, Higgins CB. Identification and localisation of ventricular septal defects by gated magnetic resonance imaging. *Am J Cardiol* 1986;**57**:1363–8.

Br Heart J 1989;62:311–4

Dilatation with progressively larger balloons for severe stenosis of the pulmonary valve presenting in the late neonatal period and early infancy

SHAKEEL A QURESHI, EDMUND J LADUSANS, ROBIN P MARTIN*

From the Departments of Paediatric Cardiology, Royal Liverpool Children's Hospital, Liverpool; and Guy's Hospital, London

SUMMARY Balloon dilatation in infants with severe pulmonary valve stenosis may not be a straightforward procedure once the arterial duct has closed. Balloon dilatation was attempted in three neonates and infants. In an 11 week old infant hypotension and bradycardia developed shortly after a 5 French end hole catheter was passed through the severely stenosed pulmonary valve. An emergency Waterston shunt was subsequently performed, but he died three days later. After this experience the technique was modified so that progressively larger balloons were used for dilatation in two infants, aged one and three weeks, with severe pulmonary valve stenosis in whom the arterial duct had closed. It was successful in both.

Percutaneous balloon dilatation is now a widely accepted treatment for pulmonary valve stenosis in children and adults.[1 2] Its application to the treatment of severe stenosis of the pulmonary valve in early infancy is less well established. There have been several reports of successful balloon dilatation in this age group.[3-7] The procedure is generally thought to be safe and effective, especially when the arterial duct is patent. When the arterial duct is closed, however, balloon dilatation may not be straightforward. The purpose of this paper is to highlight the complications associated with this procedure and to suggest modifications of technique for avoiding these complications.

Patients and methods

Percutaneous balloon dilatation was attempted for severe pulmonary valve stenosis in three neonates and infants. The group consisted of an 11 week old boy (born at 32 weeks' gestation) (case 1), a one week old boy (case 2), and a three week old girl (case 3) (table).

Case 1 required assisted ventilation for 25 days after birth because of hyaline membrane disease. His chest radiograph then showed cystic changes caused by pulmonary interstitial emphysema in the right lung. He was referred because of a harsh ejection systolic murmur associated with congestive cardiac failure. Non-invasive studies with cross sectional and Doppler echocardiography showed severe pulmonary valve stenosis with an estimated transvalvar gradient of 81 mm Hg, which increased to 144 mm Hg over the next three weeks.

Case 2 presented with congestive cardiac failure and non-invasive investigations showed severe pulmonary valve stenosis with an estimated transvalvar gradient of 81 mm Hg.

Case 3 presented with mild cyanosis and breathlessness. Investigations showed severe pulmonary valve stenosis and a transvalvar gradient of 115 mm Hg.

TECHNIQUE OF CARDIAC CATHETERISATION AND BALLOON DILATATION

Cardiac catheterisation was performed percutaneously by the femoral venous and arterial routes under general anaesthesia. After measurement of the intracardiac saturations and pressures, right ventricular angiography was performed in all the patients. This confirmed a severely stenosed pulmonary valve. The pulmonary valve "annulus" was measured on the lateral projection of the angiogram. The dimensions of the angiography catheter were

Requests for reprints to Dr Shakeel A Qureshi, Department of Paediatric Cardiology, Guy's Hospital, St Thomas Street, London SE1 9RT.

*Present address. Bristol Royal Hospital for Sick Children, St Michael's Hill, Bristol BS2 8BJ

Accepted for publication 17 May 1989

Table *Data on three infants treated with balloon dilatation*

Case	*Age at BD (wk)*	*Weight at BD (kg)*	*RV systolic pressure at cath (mm Hg)*	*LV systolic pressure at cath (mm Hg)*	*RV:LV systolic ratio*	*PVA (mm)*	*B:A ratio*
1	11	2·4	240	120	2	—	—
2	1	4·2	125	95	1·3	9	1·4
3	3	3·7	135	85	1·6	8	1·25

B:A, balloon:annulus ratio; BD, balloon dilatation; LV, left ventricle; PVA, diameter of pulmonary valve "annulus"; RV, right ventricle; cath, catheterisation.

used to calculate the magnification factor. The arterial duct was closed in all three patients. The haemodynamic data are given in the table.

In case 1, a 5 French multipurpose end hole catheter was passed into the right ventricle. The patient remained haemodynamically stable while attempts were made to cross the pulmonary valve. Eventually, after the valve was crossed with a tip deflector wire in the catheter, the catheter was rapidly positioned in the proximal left pulmonary artery. The gradient across the pulmonary valve was 220 mm Hg. A 0·018 inch diameter floppy tipped exchange guide wire was quickly introduced through the catheter and placed in the distal left pulmonary artery. The patient developed rapidly progressive bradycardia and hypotension with pronounced ST segment depression on the electrocardiogram. The catheter was withdrawn to the right atrium, leaving the guide wire in the pulmonary artery, while external cardiac massage was started. Bradycardia persisted and so the guide wire was also removed. Subsequently, a stable cardiac rhythm was achieved but the infant remained hypotensive and hypoxic. An emergency Waterston shunt was performed, but he remained hypotensive and died three days later.

Necropsy confirmed severe pulmonary valve stenosis (figure) with a pulmonary valve orifice diameter of 1·5–2 mm (the external diameter of the catheter used was 1·7 mm). There was considerable hypertrophy of the right ventricle with muscular narrowing of the outflow tract. The arterial duct was closed.

After the complications encountered in case 1, we modified the technique of balloon dilatation. The pulmonary valve was initially crossed with a 0·014 inch floppy exchange guide wire (Schneider-Shiley AG) in case 2 and 0·018 inch floppy exchange guide wire in case 3. But because it was not possible to pass a 5 French end hole catheter over the guide wire through the valve orifice without causing hypotension, arterial desaturation, and bradycardia, a 4 French end hole catheter (William Cook, Europe) was manipulated over the guide wire into the proximal left pulmonary artery in case 2 and into the distal left pulmonary artery in case 3.

In case 2, a 3 mm diameter low profile coronary angioplasty balloon catheter on 4·3 French shaft (Meadox Surgimed) was passed over the guide wire and the pulmonary valve orifice was dilated. This resulted in subsequent easier positioning of the 4 French end hole catheter in the distal left pulmonary artery, where a 0·018 inch exchange guide wire was placed. This facilitated the passage of progressively larger catheters (5 French), guide wires (0·020 inch and 0·035 inch) and balloon catheters across the pulmonary valve. Dilatations were performed with 5, 8, 10, and finally 13 mm diameter balloon catheters (Schneider Medintag AG). The constriction caused by the stenosed valve was completely abolished by the last balloon inflation.

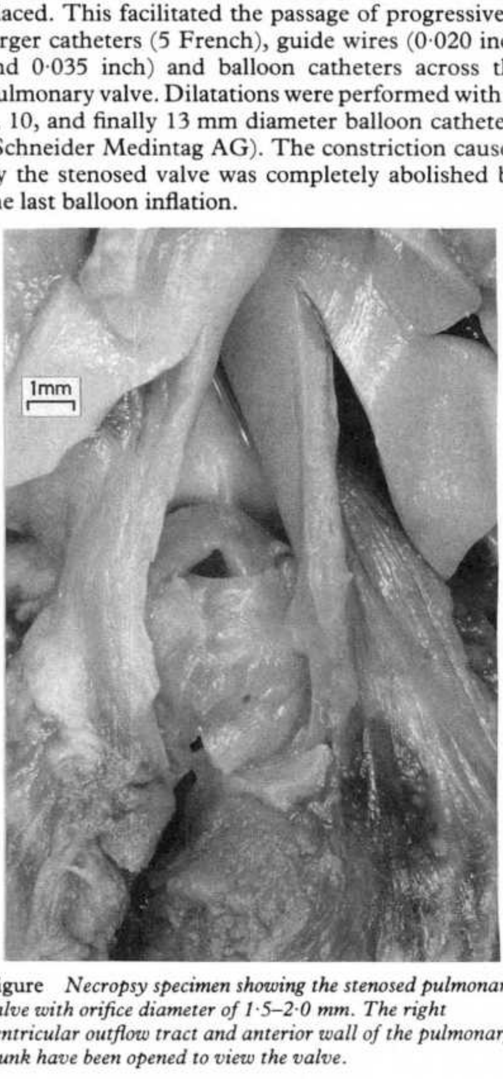


Figure *Necropsy specimen showing the stenosed pulmonary valve with orifice diameter of 1·5–2·0 mm. The right ventricular outflow tract and anterior wall of the pulmonary trunk have been opened to view the valve.*

In case 3, a 4·2 mm diameter balloon catheter on 4·3 French shaft (Schneider-Medintage AG) was positioned across the pulmonary valve and the balloon was inflated several times. The balloon catheter was replaced by a 5 French end hole catheter and a 0·021 inch exchange guide wire was positioned in the distal left pulmonary artery. This allowed a 6 mm diameter balloon catheter on a 5 French shaft (Schneider-Medintag) to be placed across the valve and the inflations repeated. Subsequently, the balloon catheter was replaced by the 5 French end hole catheter and the guide wire by a 0·035 inch exchange guide wire. A balloon catheter of 10 mm diameter on a 7 French shaft (Schneider-Medintag) was advanced over the wire and the inflations repeated until the constriction of the pulmonary valve was abolished. Both the patients were electively ventilated after the procedure for 24–48 hours.

Results

In cases 2 and 3, the procedure was well tolerated with only transient hypoxia, bradycardia, and hypotension with each balloon dilatation. Four different sized balloons were used in case 2 and three in case 3.

At the end of the procedure, in case 2, the right ventricular systolic pressure was 45 mm Hg compared with the femoral artery systolic pressure of 90 mm Hg. The peak to peak systolic pressure gradient across the pulmonary valve was 15 mm Hg. In case 3, the pulmonary artery pressure was 25/13 mm Hg and the right ventricular systolic pressure was 125 mm Hg; the gradient across the right ventricular outflow (at infundibular level) was 100 mm Hg. The brachial artery systolic pressure was 95 mm Hg.

Case 2 was discharged home four days and case 3 two weeks after balloon dilatation. In case 3, serial Doppler studies showed a gradual reduction in the transvalvar gradient to 16 mm Hg before discharge.

At the latest follow up, in each patient eight months after balloon dilatation, both the infants were symptom free and thriving. Doppler ultrasound showed an estimated residual gradient across the pulmonary valve of 13 mm Hg in case 2 and 16 mm Hg in case 3.

Discussion

Balloon dilatation of the pulmonary valve for pulmonary valve stenosis is reported to be safe and effective in neonates, infants, and children.[3-6] The first case in this report shows the difficulties and potential hazards of passing a catheter through a severely stenosed pulmonary valve. In the early neonatal period a patent arterial duct provides an alternative source of pulmonary blood flow when the pulmonary valve orifice is occluded by a catheter or an inflated balloon. This may not be the case in the late neonatal period and early infancy, when the arterial duct has closed. It is in this group of patients that balloon dilatation may be less than straightforward. Nevertheless, the problems are not insurmountable and can be overcome by technical modifications.

Manoeuvring of the catheter across the severely narrowed pulmonary valve can prove difficult. In such patients, small diameter floppy guide wires are invaluable for the rapid placement of the wire and the catheter across the valve. Shortly after the catheter was placed in the pulmonary artery in case 1, the infant deteriorated haemodynamically. We believe that this was the result of total occlusion of the valve orifice by the catheter. Necropsy did not show any evidence of trauma to the outflow tract or pericardial tamponade. The orifice diameter of the pulmonary valve was similar to the external diameter of the catheter. The choice of the optimum treatment in this infant was difficult. In view of the severe right ventricular hypertension, a closed arterial duct and, in particular, the severe lung abnormalities, we considered it preferable to attempt percutaneous balloon dilatation rather than operation. It is debatable whether a surgical approach would have been advantageous.

Our experience with case 1 prompted us to modify our technique. In the next two cases the pulmonary valve was crossed with a 0·014 or 0·018 inch guide wire and an end hole catheter, usually of 4 French size, was only manoeuvred across the valve to help position the guide wire quickly in the distal left pulmonary artery and the catheter was then rapidly withdrawn to the right atrium, thus preventing any appreciable obstruction of the pulmonary blood flow. In both cases 2 and 3, we were unable to advance a 5 French end hole catheter through the pulmonary valve orifice. The first balloon inflation, we believe, is of crucial importance to the safety and the success of the rest of the procedure. We attempted dilatation initially with a smaller diameter (3 mm) coronary angioplasty or 4·2 mm diameter balloon catheter. This resulted in an increase in the valve orifice to effectively twice its original diameter, thus reducing the risks of compromising the pulmonary blood flow and facilitating the passage of subsequent balloon catheters. After this, we dilated the valve with balloon catheters of gradually increasing diameter.

It is conceivable that, in case 2, a satisfactory outcome could still have resulted with dilatation up to the 10 mm diameter (balloon to "annulus" ratio of 1·1) balloon rather than 13 mm (ratio 1·4), thus reducing the cost of the procedure. However, we set out to achieve a final balloon to "annulus" ratio of 1·2–1·4. While a balloon to "annulus" ratio of $< 1{\cdot}0$ may be effective initially, Rao reported that residual transvalvar gradients were significantly lower if the balloon to "annulus" ratio was $> 1{\cdot}0$.[8] Furthermore, even with a ratio of 1·0–1·2, recurrence of pulmonary valve stenosis requiring repeat balloon dilatation was more likely than when the ratio was 1·2–1·4. In both cases 2 and 3 the excellent initial results have been maintained. In this age group, we found that progressive balloon dilatation was better than attempting to dilate the valve with one balloon 20–40% larger than the "annulus".

Our cases highlight the difficulties and complications associated with the management of severe stenosis of the pulmonary valve in early infancy when the arterial duct has closed. We believe that with attention to the technique and by using smaller floppy guide wires and smaller balloon catheters, of gradually increasing size, balloon dilatation can be safely and effectively performed in patients with severe pulmonary valve stenosis presenting in the late neonatal period and early infancy.

We are grateful to Miss Roxane McKay, who performed the shunt operation in case 1 and to Dr Audrey Smith for her comments on the necropsy and assistance with the photography of the specimen of the same case.

References

1 Kan JS, White RI Jr, Mitchell SE, Anderson JH, Gardner TJ. Percutaneous transluminal balloon valvuloplasty for pulmonary valve stenosis. *Circulation* 1984;**69**:554–60.

2 Kveselis DA, Rocchini AP, Snider AR, Rosenthal A, Crowley DC, Dick M. Results of balloon valvuloplasty in the treatment of congenital valvar pulmonary stenosis in children. *Am J Cardiol* 1985;**56**:527–32.

3 Rey C, Marache P, Francart C, Dupuis C. Percutaneous transluminal balloon valvuloplasty of congenital pulmonary valve stenosis with a special report on infants and neonates. *J Am Coll Cardiol* 1988;**11**:815–20.

4 Zeevi B, Keane JF, Fellows KE, Lock JE. Balloon dilatation of critical pulmonary stenosis in the first week of life. *J Am Coll Cardiol* 1988;**11**:821–4.

5 Tynan M, Baker EJ, Rohmer J, *et al.* Percutaneous balloon pulmonary valvuloplasty. *Br Heart J* 1985;**53**:520–4.

6 Sullivan ID, Robinson PJ, Macartney FJ, *et al.* Percutaneous balloon valvuloplasty for pulmonary valve stenosis in infants and children. *Br Heart J* 1985;**54**:435–41.

7 Radtke W, Keane JF, Fellows KE, Lang P, Lock JE. Percutaneous balloon valvotomy for congenital pulmonary stenosis using over-sized balloons. *J Am Coll Cardiol* 1986;**8**:909–15.

8 Rao PS. Further observations on the effect of balloon size on the short term and intermediate term results of balloon dilatation of the pulmonary valve. *Br Heart J* 1988;**60**:507–11.

Br Heart J 1989;62:315–9

The natural course of supravalvar aortic stenosis and peripheral pulmonary artery stenosis in Williams's syndrome*

NIELS G GIDDINS, JOHN P FINLEY, MAURICE A NANTON, DOUGLAS L ROY

From the Cardiology Department, Izaak Walton Killam Children's Hospital, Halifax, Nova Scotia, Canada

SUMMARY The haemodynamic findings from two serial cardiac catheterisations in ten patients with Williams's syndrome were reviewed. The median ages at study were one and nine years. Raised mean (SD) left ventricular peak systolic pressures associated with supravalvar aortic stenosis increased significantly with time from 121 (25) mm Hg to 153 (29) mm Hg. The peak systolic pressure drop between the left ventricle and aorta (measured in seven patients) increased significantly from 25 (25) mm Hg to 50 (35) mm Hg. Raised right ventricular peak systolic pressure associated with peripheral pulmonary artery stenosis (in eight patients) decreased significantly with time from 52 (26) mm Hg to 28 (6) mm Hg.

Supravalvar aortic stenosis in Williams's syndrome seems to progress rapidly, and careful monitoring is indicated. There is a strong likelihood that peripheral pulmonary artery stenosis in Williams's syndrome will improve spontaneously with time.

Williams's syndrome is characterised by unusual facies, abnormal growth and development, and variable cardiovascular anomalies. The most common of these are supravalvar aortic stenosis and peripheral pulmonary artery stenosis; but other lesions have been described, including pulmonary valve stenosis, septal defects, and peripheral systemic arterial stenosis.[1]

Studies of the natural course of these cardiovascular anomalies are limited.[2,3] We report the results of serial cardiac catheterisation in ten patients with Williams's syndrome who had supravalvar aortic stenosis or peripheral pulmonary artery stenosis or both.

Patients and methods

The ten patients were referred to and followed at the Izaak Walton Killam Children's Hospital in Halifax, Nova Scotia. These were all of the patients in whom two cardiac catheterisations were indicated because of clinically important cardiovascular lesions, usually shown by grade 4/6 cardiac murmurs or electrocardiographic findings typical of ventricular hypertrophy.

All had the characteristic features of Williams's syndrome, including distinctive facies and developmental delay. None had cardiovascular symptoms, and there was no contributory family history. Table 1 shows the age and sex of these patients. Six of them were boys.

Table 1 *Study group*

		Age (yr)	
Patient	*Sex*	*Cath 1*	*Cath 2*
1	F	1 yr	9 yr 8 mth
2	M	10 mth	8 yr 8 mth
3	F	10 mth	10 yr 5 mth
4	M	4 yr	11 yr 2 mth
5	F	8 yr 4 mth	13 yr 7 mth
6	M	1 yr 2 mth	8 yr 6 mth
7	M	3 yr 11 mth	8 yr 8 mth
8	M	2 yr 1 mth	6 yr 7 mth
9	M	11 mth	4 yr 4 mth
10	F	8 mth	9 yr 4 mth
Mean		2 yr 5 mth	9 yr 1 mth
Median		1 yr	9 yr

Cath, catheterisation.

Requests for reprints to Dr Niels G Giddins, Variety Children's Heart Centre, 685 William Avenue, Winnipeg, Manitoba R3E OZ2, Canada.

*Presented in part at the 59th Scientific Sessions of the American Heart Association, Dallas, Texas, USA in 1986.

Accepted for publication 11 April 1989

Table 2 *Left heart haemodynamic function*

	Left ventricular (LV) peak systolic pressure (PSP) (mm Hg)		*Aortic (Ao) PSP (mm Hg)*		*LV-Ao PSP gradient (mm Hg)*	
Patient	*Cath 1*	*Cath 2*	*Cath 1*	*Cath 2*	*Cath 1*	*Cath 2*
1	130	156	96	82	34	74
2	100	170	N/A	135	N/A	35
3	110	142	110	104	0	38
4	170	200	105	82	65	118
5	90	135	90	135	0	0
6	83	150	83	75	0	75
7	140	175	84	95	56	80
8	120	145	100	115	20	30
9	140	174	N/A	128	N/A	46
10	130	87	N/A	82	N/A	5
Mean (SD)	121 (25)	153 (29)	95 (10)	103 (22)	25 (25)	50 (35)

N/A, not available.

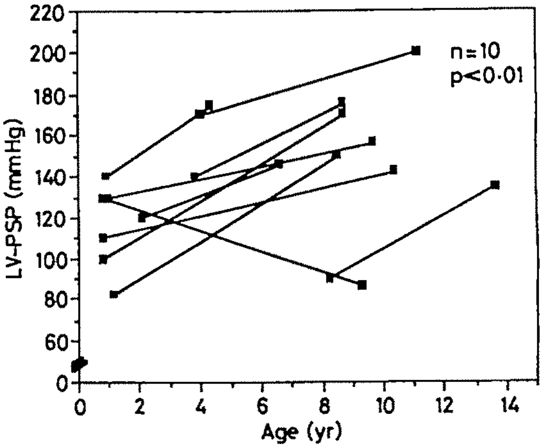


Fig 1 *Left ventricular peak systolic pressure (LV-PSP) in ten patients according to age at catheterisation. Each line represents the change in an individual patient.*

Cardiac catheterisation and angiography were performed after sedation and local anaesthesia. Left ventricular peak systolic pressure was measured during both catheterisations in all 10 patients, and pressure drops in peak systolic pressures between the left ventricle and aorta were measured in both catheterisations in seven (table 2). Right ventricular peak systolic pressure was measured during both catheterisations in eight patients, and the pressure drops in peak systolic pressure between the right ventricle and the peripheral pulmonary artery were measured in five (table 3). The mean ages at first and second catheterisations were 2 years 5 months and 9 years 1 month, respectively (table 1). Median ages were one and nine years.

For statistical analysis we used a paired *t* test.

Results

Left ventricular peak systolic pressure increased significantly with time, from a mean of 121 mm Hg (range 83–170 mm Hg) to a mean of 153 mm Hg (range 87–200 mm Hg) (p < 0·01). In only one patient (case 10) did the pressure decrease (fig 1). Aortic pressures were not measured during three initial catheterisations in infants, so serial data on the peak systolic pressure gradient between the left ventricle and aorta were available for only seven patients. There was a significant increase with time, from a mean value of 25 mm Hg (range 0–65 mm Hg) to a mean of 50 mm Hg (range 0–118 mm Hg) (p = 0·01). In no case did the gradient decrease, although in one patient no gradient was apparent at either study (fig 2). Left ventricular angiography showed a significant degree of supravalvar aortic deformity in all patients, whether or not there was a pressure gradient (fig 5).

There was a significant decrease in right ventricular peak systolic pressure with time, from a mean of 52 mm Hg (range 16–96 mm Hg) to 28 mm Hg (range 20–38 mm Hg) (p < 0·05). In one case only was there an increase of pressure with time

Table 3 *Right heart haemodynamic function*

	Right ventricular (RV) peak systolic pressure (PSP) (mm Hg)		*Main pulmonary artery PSP (mm Hg)*		*Peripheral pulmonary artery (PPA) PSP (mm Hg)*		*RV–PPA PSP gradient (mm Hg)*	
Patient	*Cath 1*	*Cath 2*	*Cath 1*	*Cath 2*	*Cath 1*	*Cath 2*	*Cath 1*	*Cath 2*
1	65	20	54	18	N/A	N/A	N/A	N/A
3	96	34	N/A	34	15 (R, L)	16 (L)	81	18
5	30	38	30	29	15 (R)	21 (L)	15	17
6	16	24	12	22	10 (L)	22 (L)	6	2
7	50	26	43	18	25 (R)	14 (R)	25	12
8	42	34	42	34	N/A	N/A	N/A	N/A
9	32	22	32	19	32 (L)	18 (L)	0	4
10	84	31	N/A	33	N/A	34 (L)	N/A	0
Mean (SD)	52 (26)	28 (6)	36 (13)	26 (7)	19 (8)	21 (6)	25 (29)	9 (7)

R, right; L, left; N/A, not available.

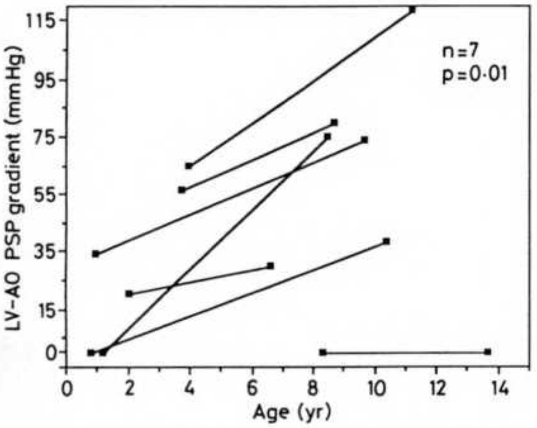


Fig 2 *Peak systolic pressure drop between the left ventricle and aorta (LV-Ao PSP) in seven patients according to age at catheterisation.*

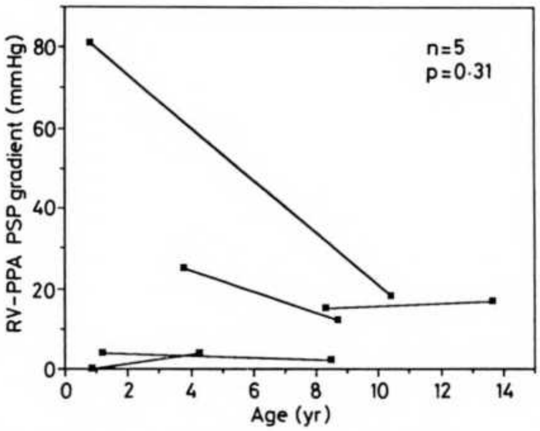


Fig 4 *Peak systolic pressure drop between the right ventricle and peripheral pulmonary artery (RV-PPA PSP) in five patients according to age at catheterisation.*

to a value greater than 30 mm Hg. The most impressive decreases were in those patients with the highest initial pressures (fig 3). Because the peripheral pulmonary arteries were not entered in three patients, serial data on peak systolic pressure gradients between the right ventricle and peripheral pulmonary artery were available only for five patients and changes were not statistically significant (fig 4).

Supravalvar aortic stenosis and peripheral pulmonary artery stenosis were the only lesions identified at catheterisation.

Decreased right ventricular pressures were associated with striking changes in the angiographic appearance of the pulmonary arteries (fig 6). At the first catheterisation of patient number 10 at nine months of age, right ventricular peak systolic pressure was 84 mm Hg and the pulmonary arteries were diffusely narrow. At the second catheterisation when the patient was nine the right ventricular peak systolic pressure had dropped to 31 mm Hg and the pulmonary arteries appeared normal.

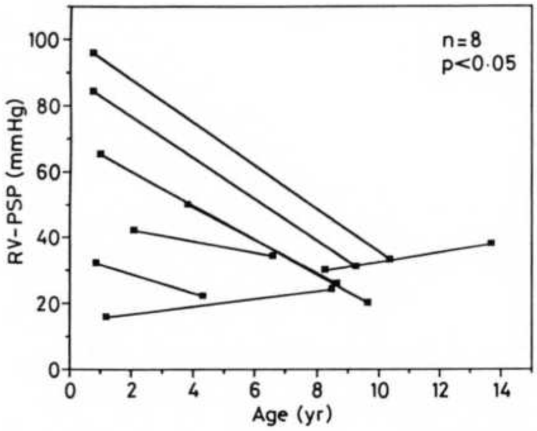


Fig 3 *Right ventricular peak systolic pressure (RV-PSP) in eight patients according to age at catheterisation.*

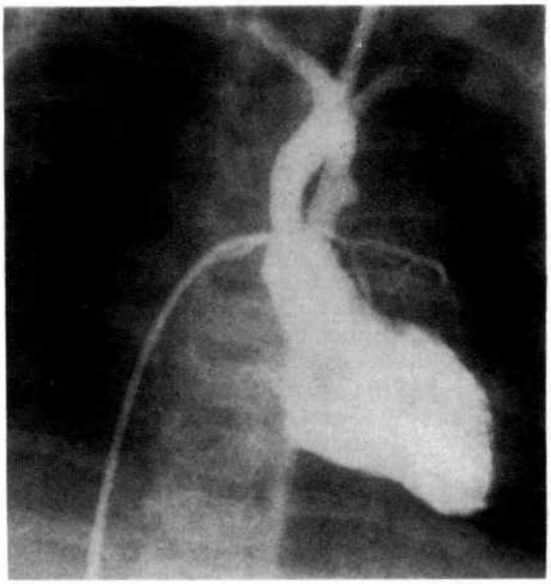


Fig 5 *Posteroanterior view of a left ventricular angiogram with the catheter through a patent foramen ovale and mitral valve. This shows distinctive supravalvar aortic narrowing with absence of post-stenotic dilatation of the ascending aorta. Considerable ventricular hypertrophy is suggested by the position of the epicardial coronary vessels. A ductus diverticulum is seen at the distal aortic arch.*

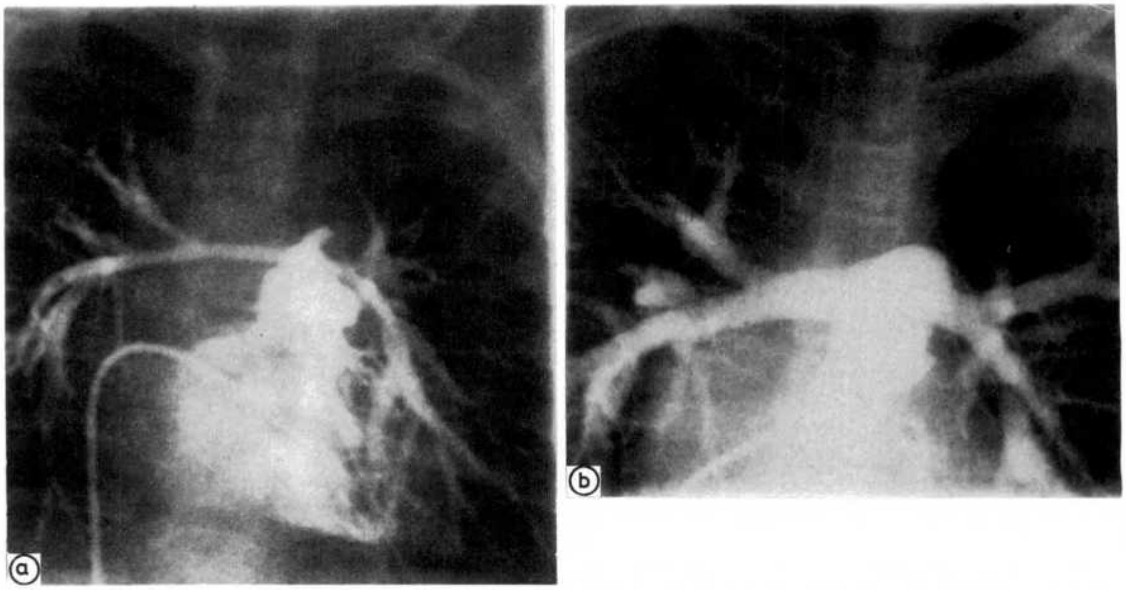


Fig 6 *(a) Posteroanterior view of a right ventricular angiogram with the catheter across the tricuspid valve. The patient (case 10) was nine months old and the right ventricular peak systolic pressure (RV-PSP) was 80 mm Hg. There is diffuse peripheral pulmonary artery narrowing. (b) Right ventricular angiogram of the same patient at nine years of age. RV-PSP was 31 mm Hg, and the pulmonary arteries appear normal.*

Discussion

In patients with Williams's syndrome subtle clinical manifestations can interfere with early diagnosis. Developmental delay and obstructive cardiovascular lesions are common in these patients and they can make both psychosocial and medical management difficult. Uncertainties about likely cardiovascular outcome can lead to inappropriate counselling of parents and inappropriate management decisions.

Our data indicate that supravalvar aortic stenosis in Williams's syndrome may be progressive and that careful monitoring of this lesion is indicated. This accords with other studies that found that obstruction of the left ventricular outlet at, above, or below the aortic valve usually increases in severity.[4] The stenotic area may actually decrease; and with body growth, increased blood flow through an unchanged stenotic area can account for higher pressure gradients.

The clinical assessment of the severity of supravalvar aortic stenosis can be difficult. In contrast with valvar lesions, there is rarely an ejection click and often murmur transmission is more prominent to the cercival area.[5] The electrocardiographic changes of left ventricular hypertrophy are present only with severe obstruction.[5] Doppler assessment of supravalvar aortic stenosis is probably reliable, but has not been studied extensively in patients with Williams's syndrome. Cardiac catheterisation remains the most valuable diagnostic technique for assessment of this lesion. This must be done with care, however, as patients with Williams's syndrome and widespread vascular or coronary involvement can be at increased risk of unexpected death at catheterisation.[6]

Our data also indicate a strong probability that peripheral pulmonary stenosis in Williams's syndrome will improve spontaneously. Decreasing right ventricular pressures with age have been reported before, and these were thought to be caused by transient obstruction of the right ventricular outflow tract.[2] We found that pressure in the main pulmonary artery was high on initial catheterisation, and this suggests more distal obstruction.

In two of the three patients with the most impressive decreases in right ventricular pressure the gradient from the left ventricle to the aorta increased over the same period. This "self-correcting" pulmonary arterial behaviour contrasts with the "progressive" aortic behaviour. Further investigation of possible mechanisms may assist efforts to treat other forms of pulmonary hypoplasia. Certainly, with the availability of dilatation procedures[7] and vascular stents[8] for treatment of arterial obstructions, knowledge of lesions that may improve spontaneously is most important.

We thank Mrs Sherrin Markiewich, Dr G W Vick III, and Dr A N Pelech for their assistance in preparing this paper.

References

1 Jones KL. *Smith's recognizable patterns of human malformation.* Philadelphia: WB Saunders, 1988:106.

2 Folger GM Jr. Further observations on the syndrome of idiopathic infantile hypercalcemia associated with supravalvular stenosis. *Am Heart J* 1977;**93**:455–62.

3 Ino T, Nishimoto K, Iwahara M, *et al.* Progressive vascular lesions in Williams-Beuren syndrome. *Pediatr Cardiol* 1988;**9**:55–8.

4 El-Said G, Galiota FM, Mullins CE, McNamara DG. Natural hemodynamic history of congenital aortic stenosis in childhood. *Am J Cardiol* 1972;**30**:6–12.

5 Friedman WF, Benson LN. Aortic stenosis. In: Adams FH, Emmanouilides GC, eds. *Moss' heart disease in infants, children and adolescents.* 3rd ed. Baltimore: Williams and Wilkins, 1983:183–5.

6 Noonan JA, Cottril CM, O'Connor WN. Supravalvular aortic stenosis. A developmental complex with an increased risk of death at cardiac catheterisation [Abstract]. *Pediatr Cardiol* 1982:**3**(4).

7 D'Orsogna L, Sandor GGS, Cullum JAG, *et al.* Successful balloon angioplasty of peripheral pulmonary stenosis in Williams syndrome. *Am Heart J* 1987;**114**:647–8.

8 Mullins CE, O'Laughlin MP, Vick GW. Implantation of balloon-expandable intravascular grafts by catheterisation in pulmonary arteries and systemic veins. *Circulation* 1988;77:188–99.

* CALCU UNIV CENTRAL LIBRARY

Br Heart J 1989;62:320–4

Family studies of congenital heart block associated with Ro antibody

WILHELMINA M H BEHAN,* PETER O BEHAN,† J M REID,‡ W DOIG,§ JAN GAIRNS†

*From the Departments of *Pathology and †Neurology, Glasgow University; ‡Department of Cardiology, Western Infirmary; §Department of Paediatric Cardiology, Royal Hospital for Sick Children, Glasgow*

SUMMARY Complete congenital heart block is associated with the presence of maternal autoantibodies to small ribosomal nucleoproteins (such as anti-Ro) which cross the placenta and may be deposited at the site of cardiac damage. Ten such cases of congenital heart block, their mothers, and their siblings were studied. The seropositive mother of one case had a similar conduction defect (bifascicular block) to that in her affected child. None of the siblings examined had cardiac lesions. Six mothers had Ro or La antibody five to 17 years after the birth of the affected child. Four mothers examined 11–32 years after the birth of an affected child were seronegative. Three of these mothers had evidence of a connective tissue disorder. This evidence is consistent with a hypothesis that a maternal viral infection, associated with autoantibody production, leads to virus crossing the placenta, damaging the fetal heart, and eliciting local deposition of maternal antibody.

The development of complete congenital heart block is associated with the transplacental passage of maternal autoantibodies directed at small ribosomal nucleoproteins.[1-3] Most mothers who give birth to an affected infant have anti-Ro or the related anti-La serum antibody, as do their infants up to three months after birth.[1 3 4] Immunoglobulins thought to be of maternal origin were found at the site of cardiac damage in one baby who died three days after birth.[2] A mother who gives birth to such an infant may or may not have a connective tissue disease at the time, but 30–60% of these women will develop such an illness subsequently.[1-5] There are, however, several unanswered questions—for example, what is the risk of subsequent offspring being affected? Are the two sexes at equal risk (affected males tend to have complete congenital heart block only while affected females show other stigmata of the neonatal lupus syndrome[5]), and, because the antibody seems to produce such severe damage to fetal myocardium, what is its long term effect on adult heart tissue?

To try and answer these questions we investigated 10 individuals who had this isolated cardiac abnormality and their mothers.

Patients and methods

CASES OF COMPLETE CONGENITAL HEART BLOCK

Table 1 gives the clinical details of the 10 cases (five male and five female patients). Six of them had had permanent pacemakers inserted. One was diagnosed in utero, four were identified in the neonatal period, and the others at ages from 18 months to 20 years. They are currently 5–32 years old.

DETECTION OF ANTIBODIES

Serum samples were stored at −70°C until use and then heat inactivated before testing. Antinuclear and anti-DNA antibodies were sought by standard indirect immunofluorescence techniques, with rat liver and *Crithidia luciliae* as the respective substrates.[6 7] Rheumatoid factor was assayed by a commercial latex agglutination test (Rheumaton) followed with an enzyme linked immunoadsorbent assay of positive samples for IgM. Antibodies to soluble cellular antigens were detected by means of saline extracts of human spleen (a potent source of Ro antigen and the other nucleoprotein complexes—Sm and nuclear ribosomal nucleoprotein (nRNP)) and fresh calf thymus (for the detection of La (SS-B)), prepared as described.[8] The serum was screened first by double immunodiffusion and then by counterimmunoelectrophoresis.[9] Known control antisera were incorporated; all positive results were confirmed by

Requests for reprints to Dr Wilhelmina M H Behan, Department of Pathology, Western Infirmary, Dumbarton Road, Glasgow G11 6NT.

Accepted for publication 9 May 1989

Table 1 *Clinical data on 10 cases of complete congenital heart block*

	Patient									
Data	*1*	*2*	*3*	*4*	*5*	*6*	*7*	*8*	*9*	*10*
Sex	M	F	M	M	F	F	M	M	F	F
Age at diagnosis	Neonate	Neonate	Neonate	In utero	18 mnth	5 yr	Neonate	3 yr	20 yr	17 yr
Pacemaker inserted	Yes	Yes	Yes	No	Yes	No	No	No	Yes	Yes
Present age (yr)	5	7	10	10	17	12	16	17	21	32

the demonstration of a complete reaction of identity with one of the positive controls, obtained with the help of Dr P J Maddison, Dr G R V Hughes, and the Center for Disease Control, Atlanta; the center also supplied anti-La, anti-nRNP, and anti-Sm antisera (antisera to related nuclear antigens). Control sera were obtained from a group of 40 pregnant women, age-matched for the mothers tested.

The Ouchterlony plates were examined at 24, 48, 72, and 96 hours. The counterimmunoelectrophoresis plates were left overnight at room temperature, then washed in 5% citrate for four hours, in saline for 48 hours, and stained with Coomassie blue.

Results

Table 2 shows the results of examining the mothers. Their ages at the time of birth of the affected child ranged from 22 years to 43 years. They are currently from five to 32 years older. Five have a connective tissue disease (1 dermatomyositis and 4 rheumatoid arthritis). The mothers of cases 1 and 5 developed severe dermatomyositis and rheumatoid arthritis respectively before any of their children were born. The other mothers (of cases 8, 9 and 10) developed arthritis after the birth of the affected infant. The mother of case 7 had rheumatic fever aged 12 years and since then has taken prophylactic antibiotics before any dental procedure.

Only the mother of case 1, who has been taking prednisolone 5 mg per day for the past 12 years, complained of cardiac symptoms—she had exertional dyspnoea. Detailed questioning elicited no complaints from the other mothers. None was hypertensive. Eight underwent electrocardiography and echocardiography. The mother of case 8 was too anxious to attend for investigation while the mother (aged 71 years) of case 10 had fallen and was unable to attend the hospital.

Table 2 *Data on the mothers of 10 cases of complete congenital heart block*

	Mother of case:									
	1	*2*	*3*	*4*	*5*	*6*	*7*	*8*	*9*	*10*
Mother's age at birth of affected child	27	29	25	31	22	25	39	43	25	39
Mother's present age with interval since the birth in brackets	32 (5)	38 (7)	35 (10)	41 (10)	39 (17)	36 (11)	55 (16)	60 (17)	46 (21)	71 (32)
Maternal illnesses	Dermatomyositis for 15 yr	—	—	—	Mild rheumatoid arthritis for 18 yr	—	Rheumatic fever aged 12 yr. Healthy since then	Moderately severe arthritis for 10 yr	Rheumatoid arthritis for a yr	Rheumatoid arthritis for 15 yr
Cardiac findings/ symptoms	Exertional dyspnoea	—	—	—	—	—	—	—	—	—
Blood pressure (mm Hg)	130/80	110/80	130/80	150/95	120/70	110/70	145/90	Not done	124/90	Not done
Electrocardiogram and echocardiogram	Normal	Bifascicular branch block	Normal	Normal	Normal	Normal	Normal	Not done	Normal	Not done
Antibodies present to Ro, La, antinuclear (ANA), rheumatoid factor (RhF)	Anti-Ro, ANA 1/1000, RhF +ve, rheumatoid IgM 1500 units/ml	Anti-Ro	Anti-Ro, RhF +ve	Anti-Ro, ANA 1/64, RhF +ve	Anti-Ro	None	Anti-La, ANA 1/1000, anti-DNA +ve	None, RhF +ve	None, RhF +ve	None

Table 3 *Family relationships in individuals with complete congenital heart block*

	Case No									
	1	2*	3	4	5*	6*	7	8	9*	10
Present age (yr)	5	7	10	10	17	11	16	17	21	32
Birth order	Youngest of 3	Second of 3	Younger of 2	Younger of 2	Elder of 2	Elder of 2	Youngest of 3	Youngest of 6	Third of 4	Youngest of 3
Siblings	Sister aged 11. Brother aged 10	Brother aged 10. Brother aged 18 mnth	Sister aged 13	Brother aged 13	Brother aged 16	Sister aged 8	Brother aged 28 Brother aged 25	Sisters aged 33, 31, and 27 yr, then miscarriage. Brother aged 23	Sister aged 26, then still-born anencephalic. Sister aged 20	Brother aged 43, then miscarriage

*Subsequent normal delivery.

The only abnormality detected was in the mother (aged 38) of case 2, who was a non-smoker and who had partial right bundle branch block with left axis deviation. She had no evidence of ischaemic heart disease. Five mothers had Ro antibody, when tested five to 17 years after delivery and one had La antibody, at 16 years after delivery. Four mothers, examined at 11 to 32 years later, were seronegative. Two years previously the same results had been found. Six mothers had a connective tissue disease with positive serology. The mothers of cases 1 and 7 had high titres (1/1000) of antinuclear antibodies, and the mother of case 7 also had DNA antibodies, indicative of systemic lupus erythematosus. Five mothers (of cases 1, 3, 4, 8, and 9) had sera positive for rheumatoid factor. None had antibodies to the related extractable nuclear antigens, Sm or nRNP.

The affected individuals (cases 5 to 10) were themselves tested for the same panel of antibodies and were, as expected, all negative.

Table 3 shows the family relationships. Each case of congenital heart block had one or more siblings. The older ones had been examined by a cardiologist at the time the index case was diagnosed and none was found to have any evidence of cardiac disease. Four families had children born after the affected child, from one to eight years later, and all of these had undergone cardiac evaluation with electrocardiograms and had been found to be normal. The other six patients were the youngest in their families; the births of three of them were preceded by miscarriages.

We looked at three generations in the family of one patient (case 9) who was herself seronegative as expected. She recently gave birth to a healthy son.

Discussion

Complete congenital heart block is a rare cardiac lesion, occurring as an isolated finding in approximately 15 of 20 000 live births,[10] but it accounts for one in 200 referrals to specialised cardiac centres and is of considerable importance since those affected require lifelong cardiac supervision, usually with the insertion of a series of pacemakers.[10] Although the condition was originally described in 1901[11] and the first case of an affected infant with a mother who had systemic lupus erythematosus was reported in 1945,[12] it was not until 1977 that the consistent relation of this heart lesion to maternal connective tissue disease was established.[13] Weston *et al* then suggested that the SS-A (Ro) antibody might be a serological marker for the neonatal lupus syndrome, including congenital heart block.[14] The suggestion was quickly confirmed by work showing that 34 of 41 mothers who had an affected infant had anti-Ro serum autoantibody, as did seven of eight of their infants.[1] Half of the mothers also had the related La antibody,[1] which may be exclusively associated with Ro but no other autoantibodies.[3] Since then, it has been postulated that the maternal autoantibody actually causes the cardiac damage, because maternal immunoglobulin, with or without complement, was found in the hearts of affected infants.[2 15]

Two questions immediately arise. What is the risk to the child of a mother who is seropositive for anti-Ro and what may be the long term effect of the antibody on the mother herself? In attempting to answer them, we concluded that the antibody itself cannot be the damaging agent although it may provide a clue to the pathogenesis.

Our group of mothers was typical of those previously described, with specific antibodies in six mothers and three of the four seronegative women having developed a connective tissue disease. They were tested 11–32 years after the birth of an affected child, which may explain their seronegativity. One mother did not have any positive immunological results but she is only 36 years old.

An unexpected finding, not previously recorded in any such mothers, was that of partial right bundle branch block with left axis deviation, indicating bifascicular conduction damage, in the mother of case 2. She was an energetic, normotensive woman of 38, a non-smoker, with no evidence of ischaemic heart disease but this result showed that she had evidence of conduction damage similar to that of her middle son. None of the other seven women had any abnormality, although the connective tissue disorders, which four of them had, are known to be associated with such cardiac lesions. These were dermatomyositis,[16 17] rheumatoid arthritis,[18] and systemic lupus erythematosus.[19] It is plain, therefore, that even in predisposed mothers, the Ro antibody may be present for up to 17 years without causing any injury to the maternal conduction system.

As for the risk to the child of a seropositive mother, all our cases had unaffected siblings—older, younger, or both. Four children, the younger siblings of cases 2, 5, 6, and 9 were undoubtedly exposed to maternal Ro antibody, while others (of cases 1, 8, 9, and 10) are likely to have been at risk. The mother of case 1 had had severe dermatomyositis (a disorder in which Ro antibodies may appear[17]) since before the birth of any of her three children, while the other mothers were each delivered of a stillbirth immediately before the birth of their affected infant. Ro antibody is undoubtedly associated with fetal loss.[1 20] In summary, the ten mothers had a total of 30 pregnancies with at least 18 fetuses exposed to Ro antibody: 10 developed heart block, three died, and five were unaffected healthy infants.

Similar anomalous findings have been reported before. They include the birth of dizygous twins, one affected and one not, and three healthy mother and infant anti-Ro seropositive pairs among 300 randomly selected pregnancies.[1 13 21] The explanations advanced previously have included possible fluctuations in antibody titre, differing maternal-fetal histocompatibility antigens[3 22] and a hormonal effect, because female infants are more commonly affected,[3 4] but none of these has been substantiated.

The most telling facts against Ro antibody being the cause of the damage, however, are that first, the antigen against which it is directed is present not only in cardiac conduction tissue but in virtually every mammalian cell,[23] including fetal tissue at 16–18 weeks' gestation[24] (the earliest stage at which heart block has been detected). Secondly, since Ro is intracellular it should not elicit an immunemediated attack—although there is a possibility that it could appear on Purkinje cell membranes at a critical developmental stage.[24]

We would like to suggest a simple explanation for the anomalies in our study and those of others, namely that, before or during the early stage of pregnancy, the mother sustains a mild, perhaps unrecognised viral infection, to which she produces Ro or La antibodies. The virus crosses the placenta and damages the infant myocardium while specific maternal antibody, also crossing the placenta, localises in the same area. The infection in the child is self-limiting but it may persist in the mother so that a series of infants are affected. The mother's own heart may also be damaged (see case 2). An obvious viral candidate is a Coxsackie virus, since these viruses are common causes of myocarditis,[25] show considerable sequence homology with certain intracellular proteins,[26] and may persist in connective tissue diseases—for example dermatomyositis[27] (see case 1).

References

1 Scott JS, Maddison PJ, Taylor PV, *et al.* Connective tissue disease, antibodies to ribonucleoproteins, and congenital heart block. *N Engl J Med* 1983;**309**: 209–12.

2 Litsey SE, Noonan JA, O'Connor WM, *et al.* Maternal connective tissue disease and congenital heart block. *N Engl J Med* 1985;312:98–100.

3 Lee LA, Weston WL. New findings in neonatal lupus syndrome. *Am J Dis Child* 1984;**138**:233–6.

4 Watson RM, Lane AT, Barnett NK, *et al.* Neonatal lupus erythematosus: a clinical, serological and immunogenetic study with review of the literature. *Medicine (Baltimore)* 1984;**63**:362–78.

5 Vetter VL, Rashkind WJ. Congenital complete heart block and connective-tissue disease. *N Engl J Med* 1983;**309**:236–7.

6 Holborrow EJ, Weir DM, Johnson GD. A serum factor in lupus erythematosus with affinity for tissue nuclei. *Br Med J* 1957;**ii**:732–4.

7 Aarden LA, de Grott ER, Feltkamp TEW. Immunology of DNA. III. *Crithidia luciliae:* a simple substrate for the determination of anti-dsDNA with the immunofluorescence technique. *Ann NY Acad Sci* 1975;**254**:505–14.

8 Venables PJW, Smith PR, Maini RN. Purification and characterization of the Sjögren's syndrome A and B antigens. *Clin Exp Immunol* 1983;**54**:731–8.

9 Bunn CC, Gharavi AE, Hughes GRV. Antibodies to extractable nuclear antigens in 173 patients with DNA-binding positive SLE: an association between antibodies to ribonucleoproteins and Sm antigens observed by counterimmunoelectrophoresis. *J Clin Lab Immunol* 1982;**8**:13–7.

10 Cobbe SM. Congenital complete heart block. *Br Med J* 1983;**286**:1769–70.

11 Morquio L. Sur une maladie infantile et familiale caractérisée par des modifications permamentes du pouls, des attaques syncopales et epileptiformes et la mort subite. *Archives de Medicine des Enfants* 1901; 4:467–75.

12 Plant RK, Steven RA. Complete A-V block in a fetus: case report. *Am Heart J* 1945;**30**:615–8.

13 Chameides L, Truex RC, Vetter V, *et al.* Association of maternal systemic lupus erythematosus and congenital complete heart block. *N Engl J Med*

1977;**297**:1204–7.

14 Weston WL, Harmon C, Peebles C, *et al.* A serological marker for neonatal lupus erythematosus. *Br J Dermatol* 1982;**107**:377–82.

15 Taylor PV, Scott JS, Gerlis LM, *et al.* Maternal antibodies against fetal cardiac antigens in congenital complete heart block. *N Engl J Med* 1986;**315**:667–72.

16 Askari AD, Huettner TL. Cardiac abnormalities in polymyositis/dermatomyositis. *Semin Arthritis Rheum* 1982;**12**:208–19.

17 Behan WMH, Behan PO, Gairns J. Cardiac damage in polymyositis associated with antibodies to tissue ribonucleoproteins. *Br Heart J* 1987;**57**:176–80.

18 Villeco AS, de Liberali E, Branchi B, *et al.* Antibodies to cardiac conducting tissue and abnormalities of cardiac conduction in rheumatoid arthritis. *Clin Exp Immunol* 1983;**53**:536–40.

19 James TN, Rupe CE, Monto RW. Pathology of the cardiac conduction system in systemic lupus erythematosus. *Ann Intern Med* 1965;**63**:402–10.

20 Hull RG, Harris EN, Morgan SH, Hughes GRV. Anti-Ro antibodies and abortions in women with SLE. *Lancet* 1983;**ii**:1138.

21 Calmes M, Bartholomew BA. SS-A (Ro) antibody in random mother-infant pairs. *J Clin Pathol* 1985;**38**:73–5.

22 Lockshin MD, Gibofsky A, Peebles CL, *et al.* Neonatal lupus erythematosus with heart block: family study of a patient with anti-SS-A and SS-B antibodies. *Arthritis Rheum* 1983;**26**:210–3.

23 Wolin SL, Steitz JA. The Ro small cytoplasmic ribonucleoproteins: identification of the antigenic protein and its binding site on the Ro RNAs. *Proc Natl Acad Sci USA* 1984;**81**:1996–2000.

24 Lee LA, Harmon CE, Huff JC, *et al.* The demonstration of SS-A/Ro antigen in human fetal tissues and in neonatal and adult skin. *J Invest Dermatol* 1985; **85**:143–6.

25 Woodruff JF. Viral myocarditis. A review. *Am J Pathol* 1980;**101**:427–529.

26 Walker EJ, Jeffrey PD. Sequence homology between encephalomyocarditis virus protein VPI and histidyl-tRNA synthetase supports a hypothesis of molecular mimicry in polymyositis. *Med Hypotheses* 1988; **25**:21–5.

27 Bowles NE, Sewry CA, Dubowitz V, *et al.* Dermatomyositis, polymyositis and Coxsackie-B-virus infection. *Lancet* 1987;**i**:1004–7.

Br Heart J 1989;**62**:325–7

British cardiology

Crisis in cardiovascular research in Britain

M F OLIVER

From the Cardiovascular Research Unit, University of Edinburgh

The central theme of this commentary is that in Britain over the past ten years progressively fewer committed research graduates, medical and non-medical, have been attracted to a career in cardiovascular science and that those of us who ought to be able to provide opportunities commensurate with the aspirations of these graduates are failing to do so. Many will find my analysis depressing.

Medical science today

There is a dearth of clinical scientists both in the United Kingdom and in North America. Why should this be?

Is it possible that fewer people are graduating from our medical schools with a sustained sense of inquiry and excitement in medical science? The examination grades demanded by most medical schools for entry into medicine have remained very high or have increased over the past two or three decades and there can be no doubt about the potential of most students. But their purpose in choosing medicine may be different now from 10 and more years ago and relate more to the security and social acceptability of being a doctor than to the less easily identifiable aim of asking and pursuing questions relating to disease. Alternatively, more of those who are stimulated by the unknown may be opting during school years for a career in the biological, molecular, or physical sciences, where the rapidity of advances and opportunities to participate in them may appear to those in their teens to be greater. Or perhaps science as a whole and its technology have become more suspect and are trusted less—with softer social issues appearing ideologically more attractive.

The weight of facts to be learned in medical school and the continuing rigidity of their teaching may so concuss many students that they find it hard to develop any independent or personally original ideas. The decreasing enthusiasm for intercalated courses in basic or paraclinical sciences is a measure of this. Whether an MB/PhD programme, currently being favoured by some in academic medicine, is an answer remains to be seen. In the future these courses are bound to provide a better scientific background than many young doctors currently have, but this may not attract them into clinical science. The American experience suggests that a larger proportion of those who complete their MD/PhD programmes may go on to pursue a career in basic science or join the pharmaceutical and other industries than those who remain in clinical medicine.

Then there are powerful competing forces. Newly qualified doctors are understandably seduced away from clinical science by the security and higher salaries offered by the National Health Service[1]: extra units of medical time for on-service rotas may increase the income of a registrar in his or her late twenties to double that of a university clinical lecturer. The enticement of private practice is an increasingly strong negative force. Industry, where research is mostly prescribed, has captured a few imaginative people but probably does not present a big challenge to the more academically minded. Then there are important areas in our profession, such as general practice, that take others away from scientific medicine.

The very demanding and heavy clinical service load is of course the most potent influence that thwarts the development of investigative interests. The busy registrar or young consultant who is inspired to ask "why" needs to have considerable passion to pursue their question in the face of this load. And too many flirt with academic medicine to improve their curriculum vitae as a means of furthering a future service career.

Added to all this, government funding of research

Requests for reprints to Professor M F Oliver, Cavendish Clinic, 21 Wellington Road, London NW8 9SQ in Britain is declining in real terms and looks set to decline further.[2] Successive government reports, including the recent White Paper, indicate that many politicians are either ignorant or dismissive of the needs of academic medicine and of clinical science. Hence the recent formation of the Academic Medicine Group.[3]

Cardiovascular science

A seduction factor that is less well recognised and that operates particularly against research into cardiovascular science is the demand of diagnostic and therapeutic technology. As Krikler recently pointed out[4] the early technical advances were crucial in starting to separate cardiology as a subspecialty in medicine. Many young graduates become interested in and expert in complex instrumentation solely because of the need to provide an up to date service. Excellent though this may be, the use of new technology should not be allowed to become a purpose on its own—or the tail that wags the dog. While there are some impressive examples of productive and innovative clinical studies based on cardiac catheterisation, angiography, echocardiography and Doppler echocardiography, and radionuclides, most of these techniques are necessary routines that take up an inordinate amount of the time and distract young doctors from developing their research interests. Sir Thomas Lewis, who described the role of clinical science,[5] knew this and wrote in 1920 "Let the knowledge of disease be built up by means of such instruments".[6] He also wrote "the special method is for the investigator into pathological processes; it is not for the pure clinician". There is an even greater need now to heed these views of nearly seventy years ago. Clinical diagnostic technology should be used more to formulate and explore new ideas.

The number of really able young cardiac scientists —men and women formally trained in cardiology and also in basic or applied science—seeking senior lectureships and chairs in cardiovascular disease has fallen in the past decade.[7] While this probably results from the seduction factors already described, the paucity of science based fellowships and of funds to support programme grants must share the blame. Senior cardiologists may also be at fault in not providing an appropriate atmosphere for innovative investigation. Some who read this article will rightly deny this charge, but many cardiologists in teaching hospitals are and have been too taken up with administration or their clinical service to encourage their younger colleagues into cardiac scientific inquiry. A broader range of senior positions should attract more people into an academic career and this relates to the need for a career structure (see later).

In the postwar years, the strength of academic cardiology in Britain lay in the fine training available in physiology and electrophysiology and, to a lesser extent, in pharmacology. A training in biochemistry was rare. For all its earlier strengths this emphasis on physiology has been one of the weaknesses of cardiac science in the 1970s and 1980s. The cardiac catheter laboratory became and remains too dominant. As a consequence, many have failed to recognise and embrace the revolutions occurring in the biochemical understanding of disease and the opportunities offered by cell biology, molecular medicine, and the new genetics. These have outpaced and are outpacing academic cardiology, but their integration into cardiovascular science is essential if we are to reduce and treat heart disease successfully. For cardiovascular science to advance, there must be new generations of enthusiastic investigators trained and skilled in these topics and willing and able to overcome traditional barriers between research and clinical specialties. Cardiology may not be an academic subject, but there must be some who are excited enough to span the increasing gap between the new biological sciences and routine patient care. It is to such investigators that we already owe the dramatic advances of identifying adrenergic receptors and of developing antagonist and agonist drugs, of recognising the functions of endothelium in vasomotor control, of devising genetically derived thrombolytic agents, of characterising lipoprotein receptors and their pharmacological manipulation, of recognising the role of the endothelium and macrophages in the development of atheroma, and of peroxidation and free radical activity in myocardial injury.

More training opportunities

A new initiative is badly needed. Resolution of the crisis will not result from infusions of soft money: these are too temporary and usually related to a specific interest of a pharmaceutical company. The British Heart Foundation has made the most outstanding and imaginative contribution to academic cardiology ever seen in Britain, with the establishment of twelve endowed professorships and university departments and seven personal chairs. It should consolidate these by helping to plan the future. The recent establishment of three non-clinical research fellowships is a start. But what is also urgently needed is the creation of more training fellowships to expose young doctors to research in cardiovascular science. The provision of about 20 fellowships with a three year tenure for those between the ages of 27 and 33 (or thereabouts) should give cardiac science the fillip it needs. Such posts should be identified by universities through the granting of honorary lectureship status and by the Joint Planning Advisory Committee. Some posts might be created in conjunction with the new Medical Research Council initiative. Programmes for training fellowships in cardiac science should be moulded to suit the aspiring interests of the holder, so that he or she may spend a year in a "research hotel" in molecular biology, cell biology, or biochemistry; in a metabolic unit; in clinical genetics; in pharmacology; in epidemiology and so on—whichever combination is appropriate to the individual. The Joint Committee on Higher Medical Training, of which I am currently chairman, has a flexible and positive policy towards unusual training programmes. The Wellcome Clinical Research Fellowships are a good model on which to build, but cardiovascular science needs dedicated training fellowships if it is to survive and contribute nationally and internationally.

A career structure is urgently needed for clinical scientists and at last—I first wrote about this in 1977[8]—the essentiality of this is being recognised and has recently been spelt out by the House of Lords Select Committee on priorities in medical research[9] and by the Academic Medicine Group.[3] Indeed, this is regarded as "the most urgent requirement for revitalising British academic medicine".[10] A career structure for clinical scientists and an expansion of posts comparable to "new blood lecturers" is a national need, and cardiac science is crying out for its share. The British Heart Foundation could also do much to advance this cause by establishing a few more tenured senior lectureships or more permanent senior research fellowships. These would act as the goal for those in training.

The future of cardiovascular science is no less exciting than it was 40 years ago. Think of the great innovations in cardiovascular disease that have taken place over the past 20 years largely by breaking orthodox boundaries of clinical research. Think of the richness of current and future questions to be addressed in atherosclerosis, the formation of and dissolution of intravascular thrombi, cardiac hypertrophy, myocardial metabolism, myocardial ischaemia, hypertension, and so on. There is no lack of questions for cardiac science. But we have to have the will to provide for future generations to invest their intellects and resources in it. All these questions need a positive and imaginative approach and require the participation of cardiovascular scientists—particularly of medically trained individuals who can pose and develop the questions along with basic scientists.

The future of cardiovascular research

We must sustain the enthusiasm of talented postgraduates for embarking on such ventures, provide them with appropriate training opportunities, and pay them commensurately with other branches of medicine. I do not believe that there will be only a few takers. If I am wrong, the next generations of cardiologists will comprise skilled service physicians and superb graduate technicians. This will not be enough to reduce the toll of heart diseases. Nor will it be enough to provide the necessary education in developing areas of cardiovascular science. Nor will excellence in clinical service be maintained. My appeal is for more to take up cardiovascular science as part of their training, for greater opportunities to be provided to gain scientific learning in subjects related to heart diseases, and for academic cardiology to be re-established as a keystone for advancing knowledge. If it is not, British cardiology will no longer be innovative.

I thank Dr Arthur Hollman for leading me into the views of Sir Thomas Lewis and Sir James Mackenzie regarding new methods and clinical practice.

References

1 Swales J. What has happened to academic medicine? *Lancet* 1986;ii:1194–6.
2 Smith R. Is research to be privatised? *Br Med J* 1988; **296**:185–8.
3 The Academic Medicine Group. Academic medicine: problems and solutions. *Br Med J* 1989;**298**:573–9.
4 Krikler DM. The roots of modern British cardiology. *Br Heart J* 1989;**62**:230–4.
5 Lewis T. The Harveian Oration on Clinical Science. *Br Med J* 1933;ii:717–22.
6 Lewis T. The relation of physiology to medicine. *Br Med J* 1920;ii:459–62.
7 Fuster V. Future of Cardiology: Science and Practice Part 4. The practice of cardiology: changes under way. *Primary Cardiology* 1986;12:69–84.
8 Oliver MF. The shrinking base of clinical science—where are tomorrow's researchers? *Eur J Clin Invest* 1977;7:1–2.
9 House of Lords Select Committee on Science and Technology. *Priorities in medical research.* London: HMSO, 1988.
10 Booth CC. The National Health Service, the universities, and the research councils: the future of academic medicine. *Br Med J* 1988;**296**:1382–6.

Br Heart J 1989;**62**:328

Notices

British Cardiac Society

The Annual General Meeting will take place in Torquay on 22 to 25 May 1990.

Aortic valve surgery

A workshop on New Trends in Aortic Valve Surgery will be held in Riyadh on 17 and 18 January 1990. For further information contact Department of Cardiovascular Diseases, King Faisal Specialist Hospital and Research Centre, PO Box 3354, Riyadh 11211, Saudi Arabia. FAX (966-1) 441-4839.

Correction

Right ventricular infarction: diagnostic accuracy of electrocardiographic right chest leads V3R to V7R investigated prospectively in 43 consecutive fatal cases from a coronary care unit *Henning Rud Andersen, Erling Falk, Dorthe Nielsen*—We regret that there is an error in this article published in the June issue (volume 61: pages 514–20). On page 518 the body of table 4 was printed incorrectly and should have read:

Table 4 *Diagnostic accuracy (%) of right chest leads in 16 patients with electrocardiographic posterior infarction. Infarct location was examined at necropsy*

	Sensitivity	*Specificity*	*Positive predictive value*	*Negative predictive value*	*Efficiency*
ST elevation ≥ 1 mm in leads.					
V3R	64 (31–89)	80 (28– 99)	88 (47– 99)	50 (16–84)	69 (41–89)
V4R	73 (39–94)	80 (28– 99)	89 (52– 99)	57 (18–90)	75 (48–93)
V5R	64 (31–89)	100 (48–100)	100 (59–100)	56 (21–86)	75 (48–93)
V6R	73 (39–94)	100 (48–100)	100 (63–100)	63 (24–91)	81 (54–96)
V7R	91 (59–99)	100 (48–100)	100 (69–100)	83 (36–99)	94 (70–99)
Q wave in V3R	36 (11–69)	80 (28– 99)	80 (28– 99)	36 (11–69)	50 (25–75)

Numbers in parentheses are 95% confidence intervals.

November 1989 Vol 62 No 5

UCM

British Heart Journal

A monthly journal of cardiology published in association with the British Cardiac Society

Changes in the flow properties of white blood cells after acute myocardial infarction *G B Nash, B Christopher, A J R Morris, J A Dormandy* **329**

Effects of xamoterol, a β_1 adrenoceptor partial agonist, in patients with ischaemic dysfunction of the left ventricle *E Vigholt-Sørensen, O Faergeman, H M Snow* **335**

The epicardial electrogram: a quantitative assessment during balloon angioplasty incorporating monophasic action potential recordings *P Taggart, P Sutton, R John, R Hayward, H Swanton* **342**

A study of nerves containing peptides in the pulmonary vasculature of healthy infants and children and of those with pulmonary hypertension *K M Allen, J Wharton, J M Polak, S G Haworth* **353**

Transvenous ablation of atrioventricular conduction with a low energy power source *E Rowland, D Cunningham, A Ahsan, A Rickards* **361**

Clinical efficacy of intravenous amiodarone in the short term treatment of recurrent sustained ventricular tachycardia and ventricular fibrillation *W Schützenberger, F Leisch, K Kerschner, W Harringer, W Herbinger* **367**

Inaccuracies in using aortic valve gradients alone to grade severity of aortic stenosis *M J Griffith, C Carey, D J Coltart, B S Jenkins, M M Webb-Peploe* **372**

HLA Antigens in idiopathic dilated cardiomyopathy *C J Limas, C Limas* **379**

Hypertrophic cardiomyopathy in identical twins *J M Reid, A B Houston, E Lundmark* **384**

Anomalous origin of one pulmonary artery from the ascending aorta: a review of echocardiographic, catheter, and morphological features *L V Fong, R H Anderson, R D Siewers, A Trento, S C Park* **389**

Case reports

Recurrent ventricular tachycardia associated with anomalous left coronary artery from the pulmonary artery in a child managed by revascularisation and map-guided endocardial resection *J M McComb, R Vincent, C J Hilton* **396**

Successful repeat percutaneous transluminal coronary angioplasty after failed coronary artery surgery for left main coronary artery dissection *D R Ramsdale, P M Schofield* **400**

Spontaneous displacement of a pacemaker electrode and its subsequent successful reimplantation *J Gialafos, A Theophilis, G Siamas* **403**

Congenital fistula between the left ventricle and coronary sinus: elucidation by colour Doppler flow mapping *J P Gnanapragasam, A B Houston, S Lilley* **406**

Heart transplantation for Churg-Strauss syndrome *D Thomson, H Chamsi-Pasha, P Hasleton* **409**

British cardiology

The Randomised Intervention Treatment of Angina (RITA) Trial protocol: a long term study of coronary angioplasty and coronary artery bypass surgery in patients with angina *R A Henderson* **412**

Correspondence **415**

Notices **416**

CALCUTTA UNIVERSITY CENTRAL LIBRARY

British Medical Association

ASTM CODEN: BHJUAV 62(5) 329–416 (1989)
ISSN 0007-0769

British Heart Journal

EDITOR Dennis Krikler   ASSISTANT EDITORS M J Davies, Kim Fox, Peter Mills
EDITORIAL COMMITTEE
Clive P Aber Kate Bull Keith Dawkins Alan B Houston Barry R Keeton Michael Marmot
Alexander L Muir Paul J Oldershaw Philip A Poole-Wilson David B Shaw
Tom Treasure David E Ward John Watkins Peter Wilde
Editor: *British Medical Journal*   Editor: *Cardiovascular Research*
TECHNICAL EDITOR Jane Dawson   EDITORIAL ASSISTANT Anne Oliver
STATISTICAL ADVISER Stephen J W Evans

Notice to contributors

Papers relating to the heart and circulation should be sent in triplicate to the Editor, British Heart Journal, BMA House, Tavistock Square, London WC1H 9JR, and be prepared according to the *Uniform requirements for manuscripts submitted to biomedical journals* (Vancouver agreement) (*Br Med J* 1988;**296**:401–5). Authors are asked to complete a copy of the checklist provided (1989;**61**:131–2 (January issue)) when submitting their manuscripts for publication. The reference number given on the acknowledgement postcard sent out by the editorial office should be quoted on all subsequent correspondence and telephone inquiries. A covering letter must be signed by all authors stating that they have seen and approved the paper and that the work has not been, and will not be, published elsewhere. All authors will be required to transfer copyright of their articles to the journal before publication. (All material for possible publication (including Letters to the Editor) *must* be typed in *double spacing* with 4 cm margins.)

Ethical standards

Authors are expected to comply with the code of ethics known as the Declaration of Helsinki. Where appropriate, manuscripts should include a statement that the research protocol has been approved by the locally appointed ethics committee and that the informed consent of the subjects has been obtained.

Case reports should convey only the essential facts of a case and the discussion and bibliography be kept to a minimum. They should have no more than three authors, should not exceed 1500 words, and include no more than two Figures.

Abbreviations should *not* be used in the text, except for mathematical calculations and units of measurement.

References must be cited precisely according to the Vancouver agreement and be typed in *double spacing*. As a general rule, no more than three references should be cited for any one statement.

Authors are responsible for the accuracy of any references cited: these should be checked at source or with the listing in Index Medicus.

Units of measurement

All haematological and clinical chemistry measurements should be given as SI units. Blood pressures should be given in mm Hg. Measurements of length, height, weight, and volume should be reported in metric units and temperatures should be reported in degrees Celsius.

Tables must be typed on separate sheets and not in the text. Titles should be provided, and all abbreviations used must be given in full in a footnote.

Illustrations (for general requirements, please refer to *Br Heart J* 1984; **51:** 1–6).

Electrocardiograms: Black and white prints only should be sent and not the original tracings. If several tracings are grouped in a single Figure only a few complexes should be shown; the width should not exceed 14 cm unless a reduction in scale is possible.

Echocardiograms: Since these will be reproduced at a width of 7 cm or less all unnecessary or irrelevant detail (such as electronic writing) should be removed. Labelling must be superimposed directly on to the print itself and only where essential be shown on an accessory drawing. Echocardiograms obtained with 30° sector scans or bistable equipment or recorded on ultraviolet paper are not suitable for publication.

Figure legends must include an explanation of all abbreviations used in the Figure.

Copyright permission to reproduce material published elsewhere must be obtained in writing and acknowledged in the manuscript.

Proofs of articles accepted for publication will be sent for the author's approval. Proof corrections should be kept to a minimum.

Notice to subscribers

British Heart Journal is published monthly. The annual subscription rates are £97.00 inland and £113.00 overseas (USA $182·00). Combined rate: *British Heart Journal* and *Cardiovascular Research* £184 inland and £214 overseas (USA $350·00). Orders should be sent to The Subscription Manager, *British Heart Journal*, BMA House, Tavistock Square, London WC1H 9JR. Orders can also be placed with any leading subscription agent or bookseller. Subscribers may pay for their subscriptions by Access, Visa, or American Express by quoting on their order the credit or charge card preferred together with the appropriate personal account number and the expiry date of the card. (For the convenience of readers in the USA subscription orders ($182) with or without payment may also be sent to British Medical Journal, Box 560B, Kennebunkport, Maine 04046. All inquiries, however, must be addressed to the Publisher in London.) **All copies are despatched by air-speed.** First class rates available on request.

COPYRIGHT © 1989 by the *British Heart Journal*. All rights reserved. No part of this publication may be reproduced, stored in a retrieval system, or transmitted in any form or by any means, electronic, mechanical, photocopying, recording, or otherwise, without the prior permission of the *British Heart Journal*.

Second class postage paid, Rahway NJ Postmaster: send address changes to: British Heart Journal c/o Mercury Airfreight International Ltd Inc, 2323 Randolph Avenue, Avenel, NJ 07001, USA.

Br Heart J 1989;62:329–34

Changes in the flow properties of white blood cells after acute myocardial infarction

G B NASH, B CHRISTOPHER, A J R MORRIS,† J A DORMANDY*

*From the Departments of Haematology,† Medicine, and *Surgery, St George's Hospital and Medical School, London*

SUMMARY Because they can obstruct blood vessels and release noxious substances, white blood cells may contribute to the development of tissue ischaemia. The flow properties of white cells were tested after myocardial infarction, by measuring the filtration rates of cell suspensions through 8 μm pore filters. Compared with mononuclear cells from age matched controls, mononuclear cells from patients with infarction showed impaired filterability within the first day after the onset of pain; this condition persisted for at least two days and by day 10 it was improved. On day 1, granulocyte filterability and the proportion showing morphological evidence of activation were nearly normal. By day 3 the flow resistance and activation had increased, but the changes seen depended on the age of the patient. The filterability and activation of granulocytes from patients aged <60 were significantly increased from day 1, whereas there were no changes in granulocytes from patients aged >60 years. Suspensions of unfractionated white cells showed changes intermediate between the mononuclear cells and granulocytes. A group of five patients who presented with chest pain but who were subsequently found not to have had an infarction showed no evidence of abnormal filterability or activation. The changes in filterability probably reflect white cell activation, which may have an adverse effect on the perfusion of the ischaemic myocardium.

It has been suggested that white blood cells, and neutrophilic granulocytes in particular, are major mediators of myocardial injury induced by ischaemia.[1] When they are activated in the microcirculation these cells cause extensive tissue damage, for example by releasing oxygen free radicals and lysosomal enzymes.[2 3] Neutrophils would be expected to invade the ischaemic myocardium as part of the inflammatory response, but they also become entrapped in capillaries in the early stages of myocardial infarction,[4] and this response may be detrimental. In animal models of the ischaemic heart the role of white cells in mediating myocardial damage was suggested when infarct size was reduced if blood was depleted of white cells[5 6] or if lipoxygenase metabolism of arachadonic acid (to form leukotrienes) was inhibited.[7]

A rheological mechanism may contribute to the trapping of white cells and to propagation of tissue injury. White cells are much more resistant to deformation than red cells and their entry into capillaries can take several seconds, giving rise to intermittent plugging even in the normal circulation.[8] In animal studies when the perfusion pressure is lowered they become entrapped in the microcirculation of skeletal muscle causing prolonged disturbance of flow.[9] Similar events were seen during experimental myocardial ischaemia in the dog. The capillaries became plugged by white cells, mainly granulocytes, and these were not dislodged by reperfusion.[4] Furthermore, reperfusion increased the number trapped, possibly owing to activation of newly arriving cells by factors released by reaction of the earlier white cells with the endothelial wall.[10] Activated cells had altered adhesive and mechanical properties,[2 11] which increased their tendency to block narrow vessels. Therefore, in ischaemia there is a potential for the establishment of an ischaemic vicious cycle of cell trapping and activation, endothelial damage with release of chemotactic factors, and further activation and trapping of new cells.

Requests for reprints to Dr G B Nash, Department of Haematology, St George's Hospital Medical School, Cranmer Terrace, London SW17 0RE.

†Present address Department of Medicine, William Harvey Hospital, Ashford, Kent TN24 0LZ

Accepted for publication 16 May 1989

To investigate this possibility we measured the flow properties of white cells at intervals after myocardial infarction in patients. Previous studies have shown that the white cells of patients with severe ischaemia of the leg have abnormal flow properties attributable to activation by factors released by the ischaemic tissue.[12] A similar process of cell activation and rheological alteration might be found after more acute myocardial ischaemia.

Patients and methods

PATIENTS AND BLOOD SAMPLING

Thirty patients were initially studied on the morning after admission to hospital with severe chest pain and a presumptive diagnosis of acute myocardial infarction (day 1, average time after start of pain = 18 hours). The diagnosis was confirmed in 25 of the patients by typical electrocardiographic changes and at least a twofold rise in the serum concentrations of cardiac enzymes; the other five had not had an infarction as judged by these criteria. Measurements were repeated two days later (in 21 patients with confirmed infarction and in five without) and approximately one week later (in 15 patients with confirmed infarction only). The age range of the patients was 34–88 years (mean (SD) 61 (11)). Fifteen age matched controls aged 36–92 (mean 56 (16)) were studied once. On every occasion, 20 ml venous blood was drawn and anticoagulated with edetic acid (1·5 mg/ml). Measurements were started within two hours of collection of the sample.

SAMPLE PREPARATION

Suspensions of white cells were prepared and their filterability was measured by a method described in detail elsewhere.[13] Briefly, unfractionated white cells were separated from 10 ml whole blood by sedimentation under gravity. After sedimentation, a small fraction of these cells was fixed in 1% glutaraldehyde for subsequent morphological examination. At the same time, 10 ml blood was fractionated by centrifugation on two density gradients. The separated fractions, mononuclear cells (mixed lymphocytes and monocytes) and granulocytes, and the unfractionated cells were washed twice in phosphate buffered saline (Dulbeco A, Oxoid, London) plus 5% plasma and 1 g/l glucose, resuspended in this medium, and counted. The cell concentration was then adjusted to 5 × 10^6/ml and filtration measurements were carried out immediately. After filtration, the remaining granulocytes were fixed with glutaraldehyde.

White cell counts and differential counts were made on a Coulter Counter model S plus IV; whole blood differential counts were done on stained blood films. Fixed unfractionated white cells and granulocytes were examined by light microscopy and the percentage with pseudopodia or cytoplasmic irregularities was counted. These non-spherical cells were classified as "active".

FILTERABILITY MEASUREMENTS

Filterability was tested by measuring the flow rate of cell suspensions through filters (Nuclepore, Pleasanton, CA) with nominal pore diameters of 8 μm (actual mean diameter 7·2 μm; manufacturer's data). A St George's Filtrometer (Carri-Med, Dorking) was used, with a constant driving pressure equal to 3 cm of water. The device measures the flow rate of the suspension as a function of the volume filtered. The flow rates are expressed relative to the flow rate of the cell free suspending medium, which was separately tested for each filter.

Three flow variables were derived as previously described[12]: the initial relative flow rate (extent of initial, rapid fall in flow rate), the slow particle resistance (subsequent rate of decrease in flow, percentage/ml), and the relative flow rate after 1 ml of the sample had been filtered. Theoretical considerations suggest that the initial relative flow rate characterises the flow resistance of the main population of rapidly flowing cells and the slow particle resistance characterises a small subpopulation of slowly flowing cells. The flow rate after 1 ml represents the contribution from both these types and also from any cells that permanently block the filter pores.

STATISTICAL ANALYSIS

Group means were compared by a two tailed Student's *t* test, and between group measurements made at different times by two tailed paired *t* tests.

Results

White cell filterability was measured on days 1, 3, and 10 after acute myocardial infarction. The filterability of granulocytes and of unfractionated white cells was lower on day 3 than on day 1; it was improved again on day 10 compared with day 3. Monocyte filterability was equally reduced on days 1 and 3 and improved on day 10. These trends were seen in each flow variable. Figure 1 shows the results for the slow particle resistance, which also shows data for controls and for five patients who presented with chest pain but who showed no enzymatic or electrocardiographic evidence of infarction. These patients had normal white cell filterability on day 1 and no significant change on day 3.

Table 1 compares the white cell filterability measured for patients on day 3 with that of controls.

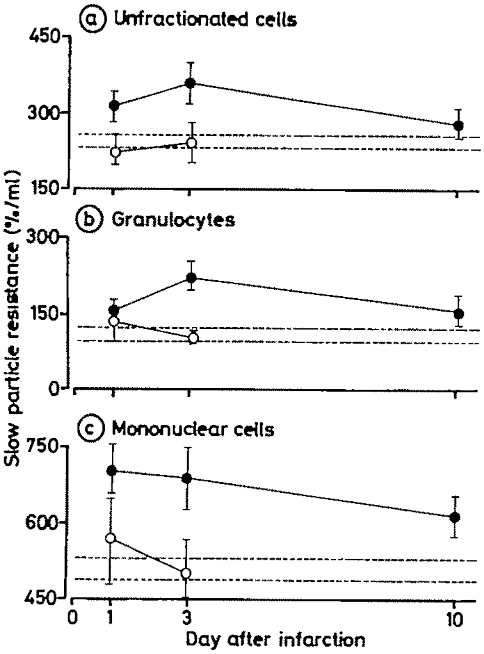


Fig 1 *Variation in white cell filterability with time after onset of pain for patients with acute myocardial infarction (●) and patients with chest pain but no infarction (○). Data on slow particle resistance are shown as the mean (SE) for (a) unfractionated white cells, (b) granulocytes, and (c) mononuclear cells. Broken lines (– – – – – –) are range of mean (SE) for controls.*

Patients with infarction had impaired filterability for each type of white cell preparation, with the trend present in all variables (initial relative flow rate decreased, slow particle resistance increased, and relative flow rate after 1 ml decreased). Some abnormalities were also evident on day 1: for unfractionated white cells the abnormalities were statistically significant ($p < 0{\cdot}05$ for each flow variable) although smaller than on day 3; for the mononuclear cells flow impairment was actually slightly greater on day 1 ($p < 0{\cdot}01$). On day 10, the filterability of granulocytes and of unfractionated cells was not significantly different from that of the controls, while the filterability of mononuclear cells had improved but remained slightly but significantly abnormal ($p < 0{\cdot}05$).

Table 1 also shows data for the percentage of white cells judged to be active by morphological criteria. Patients with myocardial infarction had more active unfractionated cells on day 3 than the controls, but not on the other days. For granulocytes, the increase in the percentage of active cells on day 3 was not significantly different from that in the controls. In individual patients, however, there was a strong, significant correlation for each flow variable on each day between granulocyte filterability and the percentage of active cells ($p = 0{\cdot}0015$, $r = 0{\cdot}763$; $p = 0{\cdot}0001$, $r = 0{\cdot}922$; $p = 0{\cdot}01$, $r = 0{\cdot}659$ for the different flow variables on day 3).

The granulocyte response after infarction was strongly dependent on the age of the patient. There was a significant inverse correlation between age and both granulocyte filterability and the percentage of active cells. Figure 2 shows day 3 data for slow particle resistance and the percentage of active granulocytes plotted against age. Initial relative flow rate and flow rate after 1 ml showed similar correlations. The correlations were present but less pronounced on days 1 and 10 (data not shown). If the patients were separated into those aged <60 and those aged >60 years, several differences were seen. Figure 3 shows the trends for slow particle resistance. Patients over 60 years had nearly constant filterability after infarction, and their flow was not significantly abnormal at any time. The younger group started at approximately the same values but con-

Table 1 *Filterability of white blood cells and percentage that are active on day 3 after infarction in 21 patients and in 15 controls (mean (SD))*

	Filterability variables			
	Initial relative flow rate	*Slow particle resistance (%/ml)*	*Relative flow rate after 1 ml*	*Active cells (%)*
Unfractionated cells:				
AMI	0·80 (0·06)	362 (178)*	0·32 (0·17)**	28 (14)**
Controls	0·83 (0·04)	238 (62)	0·49 (0·07)	13 (5)
Granulocytes:				
AMI	0·82 (0·05)	202 (145)*	0·45 (0·23)*	30 (26)
Controls	0·84 (0·03)	112 (46)	0·59 (0·12)	20 (20)
Mononuclear cells:				
AMI	0·66 (0·12)**	692 (217)**	0·18 (0·11)**	—
Controls	0·82 (0·09)	523 (69)	0·32 (0·06)	—

Statistical comparisons are patients *v* controls: *p < 0·05, **p < 0·01. AMI, acute myocardial infarction.

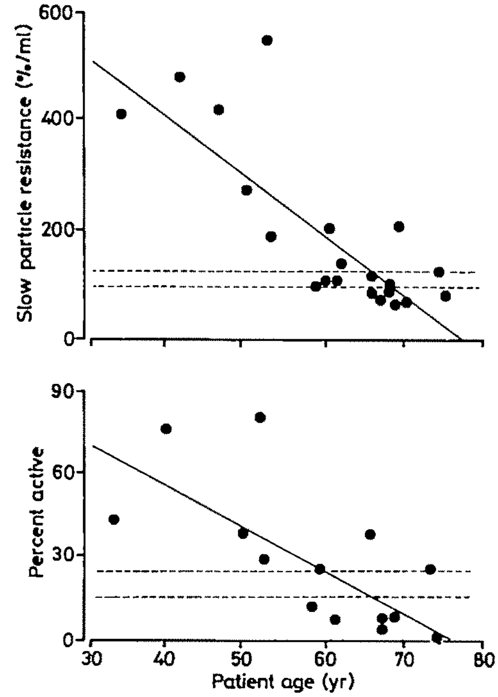


Fig 2 *Variation in granulocyte properties on day 3 with age of patients with an acute myocardial infarction. The lines were fitted by linear regression There was a statistically significant inverse correlation of slow particle resistance and percentage of active cells with patient age ($p < 0{\cdot}01$ and $r = 0{\cdot}80$ and $r = 0{\cdot}69$ respectively). Broken lines (------) are range of mean (SE) for controls.*

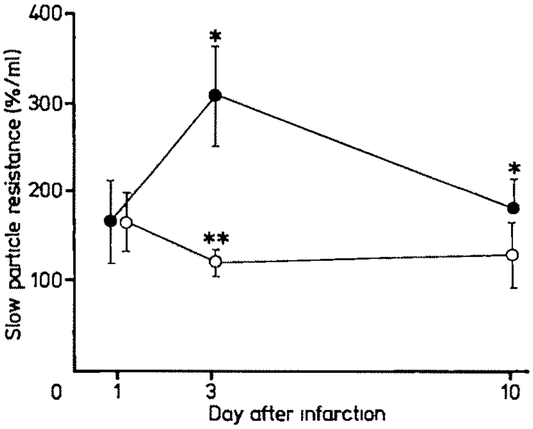


Fig 3 *Filterability of granulocytes from patients with infarctions who were ≥60 years old (○) and those ≤60 years old (●). Data are mean (SE) for the slow particle resistance plotted against the day after infarction (onset of pain). *p < 0·05 for data obtained on each day compared with the previous one. **p < 0·01 for comparison of patients > and ≤60 years old.*

Table 2 *Haematological indices (mean (SD)) after acute myocardial infarction*

Time after infarction	*White cell count (10^9/l)*		*Differential (%)*					
			Granulocytes		*Lymphocytes*		*Monocytes*	
Day 1 (n = 25)	11 9	(3·2)**	80	(10)**	14	(8)**	5	(3)
Day 3 (n = 21)	9 8	(3 7)**	71	(9)**	22	(8)**	7	(3)
Day 10 (n = 15)	9 4	(3·5)*	68	(8)*	26	(7)*	6	(3)
Controls (n = 15)	7 0	(1 5)	62	(7)	32	(7)	6	(2)

Statistical comparisons are between patients and controls. *p < 0 05; **p < 0 01.

siderable impairment developed by day 3 when each flow variable was statistically different from that in the controls and older patients. Their filterability then improved toward normal values by day 10.

The correlation between age and the filterability of mononuclear cells was less. Patients aged <60 years showed a consistently slower flow, but the difference was only barely significant (≥0·033 for the different flow variables). In the controls there was an opposite tendency towards a lower flow and greater activation with increasing age but this was not statistically significant.

Haematological indices were also abnormal in the patients (table 2). On day 1 the white cell count and the percentage of granulocytes were higher and the percentage of lymphocytes was lower than in the controls. Subsequently these variables returned towards normal.

Discussion

We found abnormalities in white cell behaviour after myocardial infarction. The granulocyte response was delayed and dependent on the patient's age. Significant impairment of flow developed by day 3 and was then inversely correlated with patient age. Generally, patients over 60 years of age showed no changes in filterability during the whole measurement period. On the other hand, patients aged ≤60 years did show significantly impaired granulocyte flow on day 3. The filterability of granulocytes correlated well with the number of "active" cells seen microscopically. Thus the changes in flow properties of granulocytes probably reflected activation, with this activation response being greater in younger patients.

The flow properties of the mononuclear cells were abnormal at the first test. Monocytes are far more resistant to flow than lymphocytes, judged both from the filterability measurements[13] and from studies of micropipette aspiration.[14] In vitro, most mononuclear cells seems to be morphologically active, and are then much more resistant to micropipette deformation than the "passive" spherical monocytes. Thus changes in the filterability of the mononuclear suspension may reflect rapid activation of the monocytes after infarction. However, the ratio of monocytes to lymphocytes in the mononuclear suspension was also increased after infarction because of the shift in white cell differential count (table 2). This ratio correlated with impaired mononuclear filterability in individual patients on day 1 but not on day 3 or day 10. Also, the ratio returned to normal more quickly than the mononuclear suspension filterability. Thus the changes in the filterability of the mononuclear suspension probably result from a combination of monocyte activation and a shift in the monocyte/lymphocyte ratio.

Unfractionated mixtures of white cells showed a response intermediate between the separated granulocytes and mononuclear cells, as might be expected. Again, filterability correlated with the number of cells judged to be morphologically active.

The dependence of the white cell response on age, which was pronounced in granulocytes but less evident in mononuclear cells, was unexpected and in the opposite direction to that found in controls (in whom dependence was weak). It was not simply the result of previous infarction. When patients who had suffered previous infarction were compared with those in a similar age range who had not had previous infarction, there were no significant differences in any of the variables of filterability (data not shown). It is possible that the cells from older patients were less able to respond to the stimulus of ischaemia and tissue damage. Previous studies have suggested that the immune response is impaired in older people.[15]

Activation, margination, and diapedesis of neutrophils occur within 60 minutes of coronary artery occlusion in dogs.[16] Margination will raise vascular flow resistance and facilitate diapedesis. Capillary plugging by granulocytes has been seen on a similar time scale of hours.[10] Plugging is thought to arise at first because the reduced perfusion pressure is not capable of deforming the white cells sufficiently for them to flow through narrow vessels. Thus rapid changes in the flow behaviour and activity of the white cells may contribute to the early stages of ischaemia and tissue damage, and could be important determinants of the final infarct size.[1] In the present study, rheological changes in white cells were seen in peripheral blood after infarction. This response probably represents a "diluted" version of what occurs in the myocardium. Also, those cells which were maximally stimulated may have become trapped and were therefore not detectable in peripheral blood. The granulocyte changes were not evident until day 3 and this could correspond to the acute phase of the inflammatory response. White cells may be involved earlier in the ischaemic process, but this was not detectable by our methods. None the less, monocyte filterability was altered from an early stage.

Because white cells are able to inhibit flow in the microcirculation, the rheological alterations seen here may worsen perfusion of the infarcted myocardium. At the same time they probably reflect functional changes in the cells, which may take part in the initiation and propagation of tissue damage. Thus treatment which inhibits white cell activation in the early stages of infarction may be beneficial, even though the normal white cell response may be essential at later stages of healing.

This work was supported by grants from the British Heart Foundation.

References

1 Lucchesi BR, Mullane KM. Leukocytes and ischaemia-induced myocardial injury *Annu Rev Pharmacol Toxicol* 1986;26:201–24.

2 Harlan JM. Leukocyte—endothelial interactions. *Blood* 1985;65:513–25.

3 Ernst E, Hammerschmidt DE, Bagge U, Matrai A, Dormandy J. Leukocytes and the risk of ischemic disease. *JAMA* 1987;257:2318–24.

4 Engler RL, Schmid-Schonbein GW, Pavelec RS. Leukocyte plugging in myocardial ischaemia and reperfusion in the dog. *Am J Pathol* 1983;111:98–111.

5 Romson JL, Hook BG, Kunkel S, Abrams G, Schork MA, Lucchesi BR. Reduction of the extent of ischemic myocardial injury by neutrophil depletion in the dog. *Circulation* 1983;67:1016–23.

6 Engler RL, Dahlgren MD, Morris DD, Peterson MA, Schmid-Schonbein GW. Role of leucocytes in response to acute myocardial ischaemia and reflow in dogs. *Am J Physiol* 1986;251:H314–22.

7 Mullane KM, Moncada S. The salvage of ischaemic myocardium by BW755C in anaesthetised dogs. *Prostaglandins* 1982;24:255–66.

8 Bagge U, Branemark P-I. White blood cell rheology. An intra-vital study in man. *Advances in Microcirculation* 1977;7:1–17.

9 Braide M, Amundson B, Chien S, Bagge U Quantitative studies on the influence of leukocytes on the vascular resistance in a skeletal muscle preparation. *Microvasc Res* 1984;27:331–52.

10 Engler RL, Dahlgren MD, Peterson MA, Dobbs A, Schmid-Schonbein GW. Accumulation of polymorphonuclear leukocytes during three hours experimental myocardial ischaemia. *Am J Physiol* 1986;251: H93–100.

11 Nash GB, Jones JG, Mikita J, Christopher B, Dormandy JA. Effects of preparative procedures on flow of white cells through micropore filters. *Br J Haematol* 1988;70:171–6.

12 Nash GB, Thomas PRS, Dormandy JA. Abnormal flow

properties of white blood cells in patients with severe ischaemia of the leg. *Br Med J* 1988;**296**:1699–701.

13 Nash GB, Jones JG, Mikita J, Dormandy JA. Methods and theory for analysis of flow through micropore filters. *Br J Haematol* 1988;70:165–70.

14 Nash GB, Meiselman HJ, Dormandy JA. Comparison of the rheological properties of different white blood cell subpopulations [Abstract]. *Clinical Haemorheology* 1987;7:433.

15 Hausman PB, Weksler ME. Changes in the immune response with age. In: Finch CE, Schneider EL, eds. *The biology of ageing*. New York: Van Nostrand, 1985: 414–32.

16 Mullane KM, Read N, Salmon J, Moncada A. Role of leukocytes in acute myocardial infarction in anesthetized dogs: relationship to myocardial salvage by anti-inflammatory drugs. *J Pharmacol Exp Ther* 1984;**228**: 510–22.

Br Heart J 1989;62:335–41

Effects of xamoterol, a β_1 adrenoceptor partial agonist, in patients with ischaemic dysfunction of the left ventricle

E VIGHOLT-SØRENSEN,* O FAERGEMAN,* H M SNOW†

*From the *Department of Internal Medicine and Cardiology, Amtssygehus, Århus, Denmark and †ICI Pharmaceuticals Division, Mereside, Alderley Park, Macclesfield, Cheshire*

SUMMARY The effects of xamoterol (200 mg twice a day) in 21 patients with left ventricular dysfunction were studied in a double blind, randomised, crossover, placebo controlled trial with treatment periods of four weeks. Most patients had moderate heart failure (New York Heart Association class II), all had ischaemic heart disease, a history of a myocardial infarction, and symptoms of dyspnoea on exertion. Patients were assessed in terms of exercise duration (bicycle ergometer), clinical signs of heart failure, symptoms and activities, and ejection fraction. Xamoterol increased exercise duration (mean (SD)) (from 445 (8) seconds to 484 (8) seconds) and ejection fraction (from 41·9 (1·3)% to 46·6 (1·3)%) and reduced the signs and symptoms of heart failure.

The results of this study show that xamoterol is a safe and effective treatment for left ventricular dysfunction resulting from ischaemic heart disease.

Treatment of patients with heart failure associated with ischaemic heart disease has conflicting goals. The use of stimulant drugs can exacerbate ischaemia particularly during exercise but the use of drugs that depress cardiac function or lower blood pressure can exacerbate the symptoms of heart failure.

Xamoterol is a β_1 adrenoceptor partial agonist with no agonist activity at the β_2 adrenoceptor.[1] The overall action of xamoterol is to stabilise the response of the heart to sympathetic stimulation such that at rest and during low levels of activity the heart receives inotropic support and during more severe exercise heart rate is reduced.[2] For these reasons xamoterol has been classified as a "cardiostabiliser".[3]

The aim of the present study was to examine the effects of xamoterol (200 mg twice a day) in a group of patients with moderate heart failure (New York Heart Association II) because of ischaemic left ventricular dysfunction.

A preliminary report of this study was made to the American Heart Association.[4]

Patients and methods

PATIENTS

Table 1 lists the characteristics of the patients. Twenty one patients (14 men and seven women; mean age 62·2 (range 44–73)) with mild to moderate heart failure entered the study. Twenty patients were in New York Heart Association class II and one was in class III. All patients had ischaemic heart disease and a history of a myocardial infarction. The main presenting symptoms were dyspnoea in 21 patients for a mean period of 24·8 months, angina pectoris in 15 patients for a mean period of 31·5 months, and fatigue in 11 patients for a mean period of 16·3 months. Six patients had had peripheral oedema for a mean period of 26·2 months. All patients had previous episodes of heart failure with pulmonary congestion. The heart was enlarged (cardiothoracic ratio > 0·5) in 16 patients.

Patients were excluded from the study if they had severe cardiac failure (New York Heart Association class IV); myocardial infarction less than two months previously; pulmonary disease causing breathlessness on exercise; sinus tachycardia exceeding 90 beats/minute; any arrhythmias requiring treatment; aortic stenosis; hypertrophic obstructive cardiomyopathy; serious renal, haemopoietic, endocrine

Requests for reprints to Dr E Vigholt-Sørensen, Department of Cardiology, Skejby Hospital, DK 8200 Århus N, Denmark.

Accepted for publication 16 May 1989

Table 1 *Data on study group*

Patient No	*Age (yr)*	*Sex*	*Cardiovascular diagnosis/history (NYHA class)*	*Drug treatment at entry (mg/day)*
1	69	F	Cardiac failure (NYHA II), previous myocardial infarction, hypercholesterolaemia	Glyceryl trinitrate, potassium chloride (1146), bendrofluazide (5)
2	52	M	Cardiac failure (NYHA III), previous myocardial infarction	Sorbide dinitrate (80)
3	72	M	Cardiac failure (NYHA II), previous myocardial infarction, ventricular aneurysm	Hydrochlorothiazide (50), amiloride (5)
4	56	F	Cardiac failure (NYHA II), previous myocardial infarction	Bendrofluazide (5), potassium chloride (1146)
5	54	M	Cardiac failure (NYHA II), previous myocardial infarction, hyperlipaemia	Bendrofluazide (5), potassium chloride (1146)
6	68	M	Cardiac failure (NYHA II), previous myocardial infarction	None
7	70	F	Cardiac failure (NYHA II), previous myocardial infarction	Bendrofluazide (2 5), potassium chloride (573)
8	61	F	Cardiac failure (NYHA II), previous myocardial infarction	Frusemide (40), potassium chloride (2250)
9	57	M	Cardiac failure (NYHA II), previous myocardial infarction	Frusemide (80) potassium chloride (2250)
10	70	M	Cardiac failure (NYHA II), previous myocardial infarction	Bendrofluazide (5), potassium chloride (1146)
11	44	M	Cardiac failure (NYHA II), previous myocardial infarction	Glyceryl trinitrate (19 5), frusemide (40), potassium chloride (2250)
12	49	M	Cardiac failure (NYHA II), previous myocardial infarction, angina pectoris	Glyceryl trinitrate (19 5), bendrofluazide (5), potassium chloride (1146)
13	46	M	Cardiac failure (NYHA II), previous myocardial infarction, hypercholesterolaemia	Glyceryl trinitrate, frusemide (40), potassium chloride (1500)
14	71	F	Cardiac failure (NYHA II), previous myocardial infarction	Hydroflumethiazide (25), potassium chloride (1146)
15	69	F	Cardiac failure (NYHA II), previous myocardial infarction, hypertension	Glyceryl trinitrate (5 2), bendrofluazide (5), potassium chloride (3396)
16	73	M	Cardiac failure (NYHA II), previous myocardial infarction	Glyceryl trinitrate (6 5), frusemide (40), potassium chloride (750)
17	62	M	Cardiac failure (NYHA II), previous myocardial infarction	Frusemide (80), potassium chloride (2250)
18	72	M	Cardiac failure (NYHA II), previous myocardial infarction	Frusemide (80), potassium chloride (2250)
19	64	F	Cardiac failure (NYHA II), previous myocardial infarction	Frusemide (40), potassium chloride (2250)
20	64	M	Cardiac failure (NYHA II), previous myocardial infarction	Frusemide (40), potassium chloride (1500)
21	64	M	Cardiac failure (NYHA II), previous myocardial infarction	Bumetanide (2), potassium chloride (2250)

NYHA, New York Heart Association.

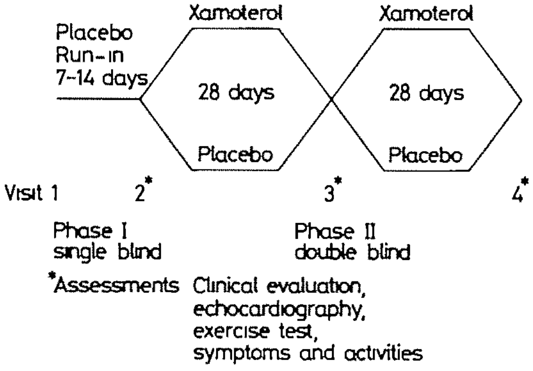


Fig 1 *Design of study.*

disorders; or mental problems and inability to complete the first three minutes of the exercise protocol; or concurrent treatment with digitalis, β blockers, vasodilators (except long acting nitrates), antiarrhythmic agents; or frusemide exceeding 80 mg daily, bumetanide exceeding 2 mg daily, or spironolactone exceeding 100 mg daily.

STUDY DESIGN

The study had two phases (fig 1). After selection at visit 1, patients entered phase 1, a single blind placebo period of seven to 14 days. Baseline assessments were carried out at visit 2. This was followed by phase II, which consisted of two double blind randomised treatment periods (placebo and

Please ask the patient the following questions and tick (✓) the appropriate box.

Do you find that you suffer from:	Never	A little of the time	Some of the time	A good part of the time	All or most of the time
Tiredness	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
Breathlessness	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
Chest Pain	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
Palpitations	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

	No difficulty	A little difficulty	Noticeable difficulty	A great deal of difficulty	
Do you find that you can walk with:	☐ 1	☐ 2	☐ 3	☐ 4	
	Very quickly	Quickly	At a medium pace	Slowly	Very slowly
Do you find that you can walk:	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

	No difficulty	A little difficulty	Noticeable difficulty	A great deal of difficulty	
Do you find that you can do your daily tasks with:	☐ 1	☐ 2	☐ 3	☐ 4	
	Very quickly	Quickly	At a medium pace	Slowly	Very slowly
Do you find that you can do your daily tasks:	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

	Never	A little of the time	Some of the time	A good part of the time	All or most of the time
Do you feel weepy/miserable/low.	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
	Very good	Good	Adequate	Poor	Very poor
Do you find that your confidence is:	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
	Very good	Good	Adequate	Poor	Very poor
Do you find that your sleeping is:	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

Fig 2 *Symptoms/activity questionnaire administered by the physician at the end of each treatment period.*

xamoterol) of four weeks in a crossover design, with assessments at the end of each period (visits 3 and 4). The dose of xamoterol was 200 mg twice a day. Concurrent treatment was maintained throughout the study (table 1). On entry to the study seven patients were taking nitrates for relief of angina pectoris and 20 patients were taking diuretics. One patient (case 6) was not taking any concurrent treatment.

The protocol was approved by the ethics committee of the Amtssygehus Århus and the study was conducted in accordance with the Declaration of Helsinki (1964). Each patient gave verbal consent to be included in the study.

ASSESSMENTS

Assessment of the patients at visit 2, 3, and 4 included the following:

Clinical examination.—Patients were examined by auscultation of the heart and lungs and for the presence of peripheral oedema, raised jugular venous pressure, and hepatomegaly.

Symptoms and activities.—The patient's "quality of life" was assessed by a series of questions about symptoms and activities. The questions were asked by the physician at the end of each treatment period and the answers were classified as one of either four or five grades (fig 2).

Echocardiography.—Patients were examined with an Aloka 710 Sector Scanner while supine or in the left reclining position. An M mode scan of the left ventricle was made at the level of the chordae tendineae. The left ventricular end diastolic diameter was measured at the time of the peak of the R wave and the end systolic diameter at the time of the peak anterior movement of the posterior wall of the left ventricle. Systolic and diastolic volumes were calculated.[5] The mitral-septal distance was also measured. The positions of the patients and the transducer were maintained as consistently as possible at each subsequent investigation.

Exercise capacity.—A symptom limited exercise test was performed on a Siemens ergometer cycle. The initial workload was 50 W; this was increased by 25 W every three minutes. During the exercise test a nine lead electrocardiogram was recorded and

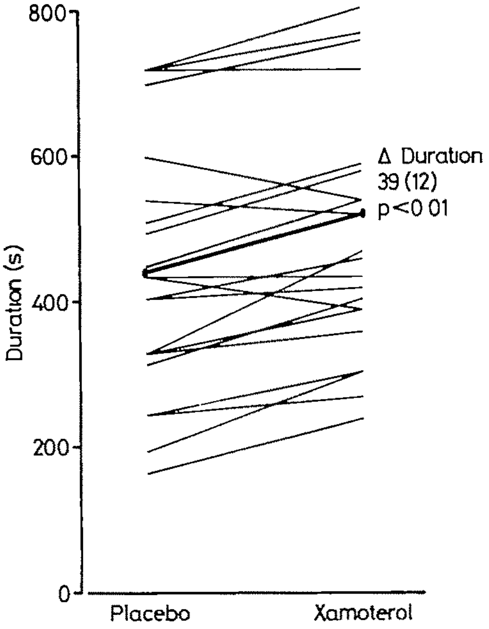


Fig 3 *Exercise duration at the end of each treatment period in 21 patients. At baseline the mean duration of exercise was 440 (37·2) seconds (not shown), after treatment with placebo it was 445 (8) seconds, and after treatment with xamoterol it was 484 (8) seconds. Exercise duration was increased in 15 patients, decreased in four patients, and remained the same in two patients.*

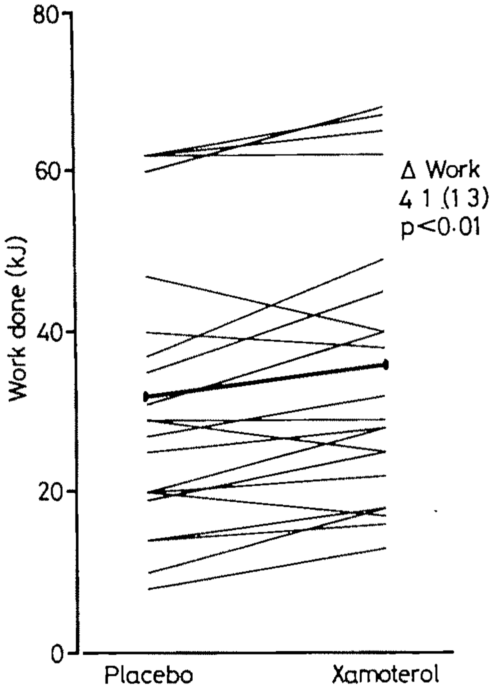


Fig 4 *Work done at the end of each treatment period in 21 patients. The adjusted mean for work done after placebo was 32·6 (0·9) kJ and after xamoterol it was 36·7 (0·9) kJ.*

evidence of myocardial ischaemia was assessed at the end of each load. Heart rate and systolic blood pressure were measured at the end of each three minute period and at maximum exercise. The duration of exercise was recorded and the total work done was calculated.

Statistical analysis.—An analysis of variance, allowing for the effects of sequence, treatment, and treatment order was used to analyse duration of exercise, work done during exercise, heart rate at maximum exercise, and ejection fraction. The Likert scores, for assessing symptoms and activities, were analysed by a non-parametric technique.

Results

EXERCISE

At baseline all 21 patients were able to achieve a work rate of 100 W; 13 patients achieved 125 W and six patients 150 W. The mean (SE) duration of exercise at baseline was 440 (37) seconds. After treatment with placebo the adjusted mean for duration was 445 (8) seconds and after treatment with xamoterol it was 484 (8) seconds. The mean difference in exercise duration between the two treatment periods (39 (12) s) was significant ($p < 0·01$). Compared with the placebo treatment, 15 patients exercised for a longer time on xamoterol treatment, two exercised for the same time, and four patients exercised for a shorter time (fig 3). The adjusted mean (SE) for work done during placebo treatment was 32·6 (0·9) kJ and that during xamoterol treatment was 36·7 (0·9) kJ—a difference of 4·1 (1·3) kJ, which was significant ($p < 0·01$) (fig 4).

Figure 5 shows the effects of xamoterol on the mean resting and exercise heart rates at each exercise load. Heart rate was reduced by xamoterol at each exercise load. The adjusted mean (SE) for heart rate at maximum exercise was reduced from 129·4 (2·1) beats/minutes (placebo) to 111·1 (2·1) beats/minutes (xamoterol) ($p < 0·001$). Figure 6 shows the effects of xamoterol on the mean systolic blood pressure at rest and at each exercise load. There was a tendency for systolic blood pressure during xamoterol treatment to be increased at rest and reduced at the higher levels of exercise. ST depression was not seen in any exercise electrocardiogram.

ASSESSMENT OF SYMPTOMS AND ACTIVITIES

Table 2 shows the results with the Likert scales. A

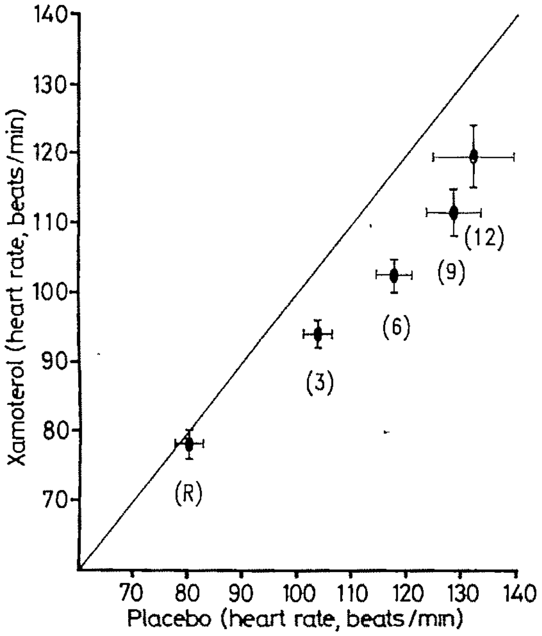


Fig 5 *Heart rates after treatment with xamoterol and placebo at rest (R) and after three, six, nine, and 12 minutes' exercise.*

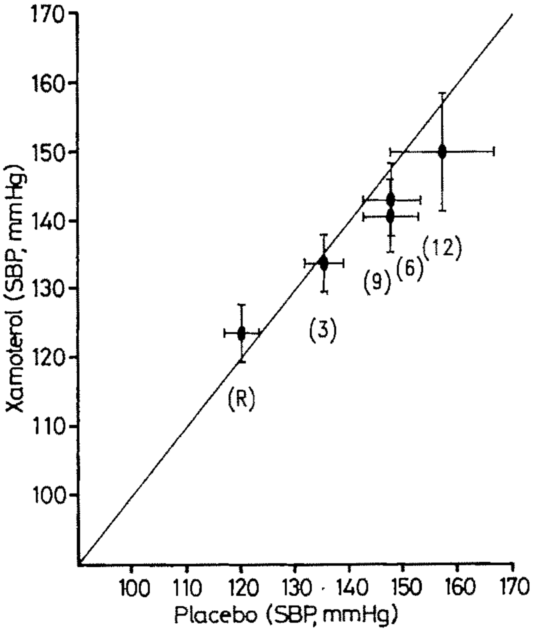


Fig 6 *Mean systolic blood pressure after treatment with xamoterol and placebo at rest (R) and after three, six, nine, and 12 minutes' exercise.*

non-parametric analysis was carried out and differences in the assessment by the physician in response to each question at the end of the two treatment periods were recorded as "better", "same", or "worse". Those patients who were not troubled by a particular symptom throughout the study were not included in the analysis. Table 2 shows the total number of patients who had each symptom and the difference between their answers at the end of each treatment period. The score for the two questions on walking, the two questions on daily tasks, and the two questions on mood were aggregated. Apart from mood, the answers to every question showed a trend in favour of xamoterol, which achieved statistical significance for breathlessness ($p < 0{\cdot}02$) and chest pain ($p < 0{\cdot}05$).

CLINICAL SIGNS OF HEART FAILURE

Each patient was examined clinically at baseline and at the end of each treatment period for the following signs of heart failure: crepitations on auscultation of the lungs, abnormal heart sounds, peripheral oedema, hepatomegaly, jugular venous distension, and irregular arterial pulse. Overall, 19 of the 21 patients had one or more signs of heart failure at baseline. The most frequent sign of heart failure was crepitations, which were found at baseline in 12 out of 21 patients, after placebo in nine, and after xamoterol in six. In two patients crepitations developed during xamoterol treatment. An irregular pulse (ventricular extrasystoles) was present in three patients at baseline, in six patients during placebo treatment, and in three patients during xamoterol treatment. The pulse became regular on treatment with xamoterol in four of the six patients who had an irregular pulse on placebo treatment. The only other sign of heart failure was jugular venous distension in two patients; this was not present after xamoterol in one patient and not present after placebo in either patient. In general, the most frequent signs of heart failure were crepitations and an irregular pulse both of which tended to be reduced during treatment with xamoterol.

ECHOCARDIOGRAPHY

Echocardiography was carried out in 17 patients at baseline and 18 patients after treatment with placebo and xamoterol. At baseline the mean (SE) ejection fraction, calculated from the end systolic and end

Table 2 *Total number of patients with each symptom or impairment of activities and the difference between treatments expressed as the number of patients feeling "better", "worse", or the "same" when treated with xamoterol*

	Total	*Better*	*Worse*	*Same*
Tiredness	20	8	2	10
Chest pain*	18	9	1	8
Breathlessness†	17	9	0	8
Palpitation	13	8	1	4
Walking	21	10	4	7
Difficulty with tasks	20	7	2	11
Mood/confidence	13	5	4	4
Sleep	9	5	2	2

*$p < 0{\cdot}05$; †$p < 0{\cdot}02$

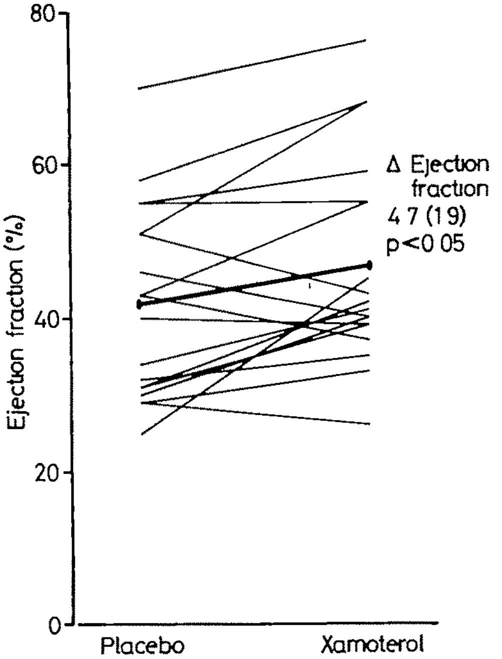


Fig 7 *Ejection fraction after treatment with xamoterol and placebo. The mean ejection fraction at baseline was 42·4 (3·4)%, after treatment with placebo it was 41·9 (1 3)%, and after treatment with xamoterol it was 46 6 (1·3)% (an increase of 4·7% (p < 0·05)).*

diastolic diameters of the heart, was 42·4 (3·4)%. After treatment with placebo the ejection fraction was 41·9 (1·3%) and after treatment with xamoterol it was 46·6 (1·3)%—an increase of 4 7 (1·9)% (p < 0·05) corresponding to a relative increase of about 12%. When patients were treated with xamoterol the ejection fraction increased in 12 patients, remained the same in one patient, and decreased in five patients (fig 7).

The improvement was independent of the initial ejection fraction; and hearts with an ejection fraction < 40% (10 patients) improved from 35·2 (2·1)% after placebo treatment to 41·3 (2·1) % after xamoterol treatment (an increase of 6·1 (3·0) % (p = 0·076), corresponding to a relative increase of about 17%).

Discussion

The patients entered into this study had mild to moderate heart failure (New York Heart Association class II and III) as a result of ischaemic heart disease. There was evidence of heart failure in all patients, despite treatment with diuretics. The mean work rates achieved (mean 120 W) were below normal for a population of similar age and sex,[6] as were the mean ejection fractions (42%). Not all patients had signs of congestive heart failure. Crepitations, which were found in 12/21 patients at baseline, were the most common sign. This low incidence of signs of congestive heart failure, despite evidence of left ventricular dysfunction, probably reflects the adequacy of treatment with diuretics.

The increase in exercise tolerance was associated with both a reduction in maximum exercise heart rate and a tendency for systolic blood pressure to be reduced. The resulting reduction in the pressure-rate product can account only in part for the prolongation of exercise in these patients with ischaemic heart disease, because there was no difference between the treatment groups in the frequency of chest pain as a reason for stopping exercise (three placebo, two xamoterol). In contrast, breathlessness was a reason for stopping exercise in most patients (20 placebo, 17 xamoterol). In patients with ischaemic heart disease symptoms of chest pain and breathlessness during a maximal exercise test may be confused. The signs and symptoms of patients in this study, however, suggest that angina was not the predominant symptom and that the patients had considerable dysfunction of the left ventricle. The mechanisms by which heart failure causes breathlessness are disputed. During maximum exercise both pulmonary wedge pressure and end diastolic pressure in the left ventricle are known to increase dramatically in patients with ischaemic heart disease and this increase has been associated with symptoms of breathlessness. Lipkin and Poole-Wilson, in an exercise protocol similar to ours, recently reported that the sensation of breathlessness was related to plasma concentrations of lactate rather than pulmonary capillary wedge pressure.[7] Sato *et al* showed that a single dose of xamoterol reduced pulmonary wedge pressure at rest and during exercise, even when heart rates were reduced.[2] These results with xamoterol are consistent with the earlier findings of Detry *et al.*[8] In both studies, during maximum exercise heart rate was reduced, cardiac output unchanged, and pulmonary wedge pressure reduced. Therefore, it is possible that prolongation of exercise tolerance in the present study is related to a delay in the acute rise in pulmonary wedge pressure. The assessment of symptoms also showed a trend for a significant reduction in breathlessness and a trend for an increase in physical activities.

The significant reduction in resting ejection fraction and the tendency for a reduction in the signs of congestion, in particular crepitations, are probably related to the modest stimulant action of xamoterol at rest and during moderate activity. In those patients who had difficulties in sleeping, xamoterol improved the quality of sleep, again an effect probably related to modest stimulation of the heart and the resulting fall in pulmonary wedge pressure.[9 10] Xamoterol is hydrophilic, does not cross the blood-brain barrier to any appreciable extent, and has no known action on the central nervous system.

In a previous study carried out in our laboratory in a selected group of patients with moderate heart failure (New York Heart Association class II and III on treatment with digoxin and diuretics), who deteriorated clinically on withdrawal of digoxin, exercise duration was on average 27% higher on digoxin and 17% higher on xamoterol.[11] In these patients there was no significant difference between the effects of digoxin and xamoterol on functional assessment score and exercise duration. More recently results in 349 patients randomised to placebo, xamoterol, or digoxin and treated for three months showed that xamoterol significantly improved exercise tolerance compared with both placebo and digitalis.[12] Patients selected for this study were similar to those in the present study. So patients with mild to moderate heart failure will benefit more from xamoterol, whereas some patients with more severe heart failure may respond better to digoxin.

The effects of xamoterol described in this study are consistent with the known pharmacology of xamoterol as a selective β_1 adrenoceptor partial agonist that modulates the sympathetic control of the heart and stabilises the response of the heart to sympathetic stimulation at about a level equal to its own intrinsic sympathomimetic activity.[1,2] Consequently, at rest or during moderate activity the heart receives additional inotropic support from xamoterol without any appreciable increase in heart rate; whereas during more severe exercise, heart rate is reduced.[8,13–15]

Evidence for this cardiostabilising activity of xamoterol in the present study comes from the increase in ejection fraction at rest with no significant change in resting heart rate and the reduction in maximum exercise heart rate. The acute effect of xamoterol in patients with left ventricular dysfunction has been described elsewhere.[8,16,17] An increase in cardiac output and a decrease in pulmonary capillary wedge pressure was reported. In three previous studies in which haemodynamic measurements were made at rest in patients with heart failure the inotropic effects of xamoterol were maintained for up to nine months.[16,18,19] These results indicate that tachyphylaxis does not occur. So both modest inotropism and the reduction of exercise heart rate are likely to be important in explaining the long term clinical benefits of xamoterol.

We found that xamoterol increased exercise duration and improved the signs and symptoms of heart failure. These changes were associated with an increase in resting ejection fraction.

We thank Margaret Day of Imperial Chemical Industries for helpful assistance.

References

1 Nuttall A, Snow HM. The cardiovascular effects of ICI 118,587: a β_1-adrenoceptor partial agonist. *Br J Pharmacol* 1982;77:381–8.

2 Sato H, Inoue H, Matsuyama T, *et al.* Hemodynamic effects of the β_1-adrenoceptor partial agonist xamoterol in relation to plasma norepinephrine levels during exercise in patients with left ventricular dysfunction. *Circulation* 1987;75:213–20.

3 Ohyagi A, Sasayama S, Nakamura Y, *et al.* Effects of ICI 118,587 on left ventricular function during graded treadmill exercise in conscious dogs. *Am J Cardiol* 1984;54 1108–13

4 Vigholt E, Faergeman O, Snow HM. Effects of xamoterol (β_1-adrenoceptor partial agonist) in patients with mild to moderate heart failure. *Circulation* 1987;76 (II) (suppl IV):IV–87.

5 Pombo JF, Troy BL, Russell RO. Left ventricular volumes and ejection fraction by echocardiography. *Circulation* 1971;43:480–90.

6 Bruce RA. Progress in exercise cardiology. In: Yu PN, Goodwin JF, eds. *Progress in cardiology.* Philadelphia: Lea and Febiger, 1974.

7 Lipkin DP, Poole-Wilson PA. Symptoms limiting exercise in chronic heart failure. *Br Med J* 1986;292: 1030–1.

8 Detry JMR, DeCoster PM, Brasseur LA. Haemodynamic effects of 'Corwin' (ICI 118,587) a new cardioselective beta-adrenoceptor partial agonist. *Eur Heart J* 1983;4:584–90.

9 White PD. *Heart disease.* New York: Macmillan, 1951.

10 Wood P. *Diseases of the heart and circulation.* London: Eyre and Spottiswoode, 1968.

11 Vigholt-Sørensen E, Sterndoff B, Andersen MF, *et al.* Digoxin and xamoterol in patients with cardiac failure. In: Endmann C, Greef K, Skou IC, eds. *Cardiac glucosides 1785–1985.* New York: Springer, 1986: 527–9.

12 von Olshausen KE. Digoxin and xamoterol compared in chronic heart failure: a double blind placebo controlled study. *Lancet* 1988;i:489–93.

13 Rousseau MF, Pouleur H, Vincent MF. Effects of a cardioselective β_1 partial agonist ('Corwin') on left ventricular function and myocardial metabolism in patients with a previous myocardial infarction. *Clin J Cardiol* 1983;51:1267–74.

14 Simonsen S. Haemodynamic effects of ICI 118,587 in cardiomyopathy. *Br Heart J* 1984;51:654–7.

15 Ikaheimo MJ, Takkunen JT. The effects of a β_1-adrenoceptor partial agonist ICI 118,587 on left ventricular function in patients with coronary heart disease. *Int J Cardiol* 1984;5:339–49.

16 Molajo AO, Bennett DH. Effects of xamoterol (ICI 117587), a new beta$_1$ adrenoceptor partial agonist, on resting haemodynamic variables and exercise tolerance in patients with left ventricular dysfunction. *Br Heart J* 1985;54:17–21.

17 Pouleur H, Rousseau MF, Mengeot P, *et al.* Improvement of global and regional left ventricular function in patients with previous myocardial infarction by a new beta$_1$-adrenoceptor partial agonist, ICI 118,587. *Eur Heart J* 1982;3 (suppl D):123–7.

18 Pouleur H, Rousseau MF, Van Eyll C, *et al.* Impaired regional diastolic function in ischaemic heart failure: pathophysiology role and beneficial effects of xamoterol. *Eur J Clin Invest* 1985; *(151/2)*: PtII, A4 ABS 22.

19 Kayanakis JG, Snow HM, Massabuau P, *et al.* Mild to moderate heart failure and 'Corwin': results at 3 and 9 months. 10th World Congress of Cardiology, Washington, 1986.

Br Heart J 1989;62:342–52

The epicardial electrogram: a quantitative assessment during balloon angioplasty incorporating monophasic action potential recordings

PETER TAGGART, PETER SUTTON,* ROY JOHN, ROGER HAYWARD, HOWARD SWANTON

*From the Department of Cardiology, The Middlesex Hospital, London and *Department of Physiology, University College and Middlesex Hospital School of Medicine, London*

SUMMARY An electrogram was recorded from the angioplasty catheter guide wire when coronary blood flow was interrupted in 20 patients undergoing percutaneous transluminal coronary angioplasty. Monophasic action potentials were recorded from the right ventricular septum together with the routine electrocardiogram. The patients were studied during angioplasty for lesions in the left anterior descending (12), circumflex (3), and right coronary arteries (6). ST elevation in the electrogram recorded in the left anterior descending and circumflex systems was usually more obvious than that in the electrocardiogram. Signals obtained from the right coronary artery were of very low amplitude and registered only minimal ST changes. The ST elevation developed in the electrogram during insertion of the catheter before inflation of the balloon in 11 of the 15 patients undergoing angioplasty of the left system. In eight of the patients showing pre-inflation ST elevation the ST shift lessened after successive inflations. Monophasic action potential recordings were obtained during 45 balloon inflations in 19 patients. In those patients undergoing angioplasty for lesions of the circumflex coronary artery the monophasic action potential showed no change during balloon inflation. In patients undergoing angioplasty for the right coronary artery the mean normalised duration at 60 seconds' occlusion was 99·6 (1·5) % of control. Of a total of 25 occlusions in the patients undergoing angioplasty for the left anterior descending coronary artery 19 showed shortening of < 5%, five showed shortening between 5 and 10%, and one showed a shortening of 16·4% in the monophasic action potential. The QT interval was satisfactorily measured in the electrogram during 36 balloon inflations, and in 24 of these it was also measured in the electrocardiogram. QT changes in the electrogram tended to be the opposite of those in the electrocardiogram. When changes in RR interval were minimal (< 20 ms) during the balloon inflation 14 of 17 electrograms showed QT prolongation but only one of 12 electrocardiograms showed prolongation. Conversely one of 17 electrograms showed shortening compared with eight of 12 electrocardiograms. There was angiographic evidence of the development of collaterals in six of 15 patients undergoing angioplasty of the left system. ST segment elevation in both the electrogram and electrocardiogram was less pronounced in these patients than in those without evidence of the development of collaterals.

ST segment changes recorded from the angioplasty guide wire provide a more sensitive index of ischaemia than the surface 12 lead electrocardiogram, and a fall in ST segments on balloon deflation is a prognostic index of a good angiographic result in the left anterior descending and circumflex arteries, but not in the right coronary artery.

Requests for reprints to Dr Peter Taggart, Department of Cardiology, The Middlesex Hospital, Mortimer Street, London W1N 8AA.

Accepted for publication 16 June 1989

Ever since Einthoven either did or did not invent the string galvanometer[1] the electrocardiogram has played a fundamental role[2] in the detection of myocardial ischaemia. Although a mainstay for on line monitoring it may be relatively insensitive to the early phase of ischaemia. The very earliest electrophysiological changes of ischaemia tend to be local to the causative lesion.[3] The initial area affected therefore tends to be small. Solid angle theory predicts that an electrode for recording an electrocardiogram would need to be placed very close to the lesion in order to identify any ischaemic changes.[4 5] This is not usually possible and the ischaemic changes that are eventually picked up by the routine electrocardiogram reflect more progressive and extensive ischaemic changes; the original local change being silent in the electrocardiogram.

The electrocardiogram is routinely used to monitor patients during percutaneous transluminal coronary angioplasty. ST segment changes are often seen during the sudden transient interruption of coronary artery blood flow when the balloon is inflated. The accuracy with which this measures the degree of ischaemia is, however, questionable. As indicated above, a recording site closer to the myocardium would be expected to register earlier changes.

The monophasic action potential recorded directly from the myocardium has been shown to provide a highly sensitive index of ischaemia.[6 7] Monophasic action potentials recorded during angioplasty from the left ventricular endocardium in the potentially ischaemic zone registered ischaemic changes in advance of the electrocardiogram in selected patients.[8] However, depending on the site of the lesion and the individual anatomy it may not always be technically possible to gain access to the centre of a potentially ischaemic zone with a catheter electrode for measuring an endocardial monophasic action potential.[9]

The tip of the guide wire used for angioplasty, however, lies close to the lesion. It has been shown that electrical signals may be transmitted via this wire thus enabling an epicardial electrogram to be recorded.[9-11] An electrogram recorded by this means has the advantage of recording near the myocardium from the territory whose native circulation is the artery undergoing angioplasty.

ST changes in the intracoronary electrogram occur in most patients during angioplasty and are generally more obvious than in the electrocardiogram.[11 12] In addition, preliminary results showed that assessment of ST segment changes in the electrogram recorded from the angioplasty guide wire during periods of balloon deflation between successive occlusions provided evidence of a good angiographic result when any initial ST elevation had subsequently been reduced by 50% at the end of the procedure.[12]

However, it is likely that any ST segment changes in the electrogram will be influenced by the development of collaterals and the dynamic behaviour of local collateral vessels in response to the ischaemic challenge and intermittent reperfusion. Furthermore, the closeness of the recording electrode to the myocardium would be expected to make it especially sensitive to the local dispersion of action potential amplitude and duration that is characteristic of early ischaemia. This may well, therefore, result in differences in the manifestation of early ischaemic change such as the ST segment and QT interval in the electrogram and the electrocardiogram. We studied simultaneous electrographic and electrocardiographic changes in the ST segment and QT interval during routine angioplasty and have related these changes to angiographic evidence of the development of collaterals.

Patients and methods

Recordings were made of the epicardial electrogram, right ventricular endocardial monophasic action potential, and the routine electrocardiogram in patients undergoing angioplasty for the relief of angina.

PATIENTS

Twenty patients were selected at random from the waiting list (table 1). Twelve were undergoing angioplasty of the left anterior descending coronary artery, three of the circumflex coronary artery, and six of the right coronary artery. One patient underwent angioplasty of both a left anterior descending and right coronary artery lesion. Table 1 gives the details of individual patients including the site and severity of the lesions. The hospital ethics committee gave approval for this study.

EPICARDIAL ELECTROGRAM

We used the angioplasty catheter guide wire as the exploring electrode to record an epicardial electrogram from within the lumen of the coronary artery. The reference electrode was positioned close to the entry point in the femoral artery. When the balloon of the dilatation catheter was positioned across the stenotic segment of the artery, the guide wire protruded about 5 cm beyond the tip of the dilatation catheter. The proximal end of the guide wire was scraped with a scalpel to remove the Teflon coating to ensure good electrical continuity.

Table 1 *Details on the 20 patients in the study*

Patient no	*Sex*	*Age*	*Vessel*	*Site*	*Collaterals*	*Result*	*ECG lead*
1	M	53	LAD	Proximal LAD at diagonal origin	None	Moderate 30–50% residual stenosis	—
2	M	46	LAD	Proximal LAD distal to 1st diagonal	Minimal if any to distal septum	Moderate 30% residual stenosis	—
3	M	62	LAD	Distal to 1st septal/diagonal	None	Moderate result dissection flap	V5
4	M	61	LAD	Distal to 1st septal proximal lesion	None	Good on proximal but distal remain	V5
5	M	48	LAD	Proximal to 1st septal	Yes	Moderate residual 40% stenosis with dissection	V5
6	F	37	LAD	Proximal to 1st septal	Yes	Good	V5
7	M	69	LAD	Lesion at 1st septal	None	Moderate 30% residual stenosis	V5
8	M	65	LAD	Proximal to diagonal distal to 1st septal	None	Good	V5
9	M	58	LAD	Distal to 1st septal	To septum posterior	Good	V5
10	M	57	LAD	Distal to 1st septal origin of diagonal	Very sparse distal on septum from RCA	Good	V5
11a	M	53	LAD	Proximal to 1st septal	Yes	Good	V5
11b			RCA	Mid RCA proximal to margin		Good	II
12	M	46	LAD	Distal to 1st septal and proximal to diagonal	Yes (late)	Good	V5
13	M	42	Cx graft	Mid Cx graft	None	Good	V5
14	M	67	Cx	Large obtuse marginal	None	Good	aVL
15	M	56	Cx	Origin of 1st obtuse marginal of Cx	None to LV surface collaterals to inferior surface in RCA territory	Good	III
16	M	62	RCA	Proximal to RV branch	None	Good	II
17	M	51	RCA	Proximal to RV branch	None	Good	II
18	M	57	RCA	Proximal to RV branch	Yes	Good	II
19	M	61	RCA	Mid RCA past RV branch	None	Good with dissection flap	II
20	F	70	RCA	Proximal to RV branch	None	Good	II

LAD, left anterior descending; Cx, circumflex; RCA, right coronary artery; RV, right ventricle.

ENDOCARDIAL MONOPHASIC ACTION POTENTIALS

Monophasic action potentials were recorded with a bipolar pressure contact silver/silver chloride catheter electrode (size 7 French) made to our specifications (Cordis). The exploring electrode (1·0 mm^2) was situated at the tip. The reference electrode (1 0 mm^2) was situated 5 mm back from the tip and was flush with the wall of the catheter. Gentle apposition of the tip electrode to the endocardium results in a monophasic action potential signal of usually 20–40 mV amplitude.

ROUTINE ELECTROCARDIOGRAM

The lead monitored as part of the routine procedure was recorded. The lead chosen was the one considered to be the most appropriate to the site of the lesion undergoing angioplasty—that is lead III for the right coronary artery; V5 for the left anterior descending coronary artery; and aVL, V5, or lead III for the circumflex, depending on which gave the best signal (see table 1).

SIGNAL PROCESSING

The electrogram and monophasic action potential signals were fed into Gould isolated preamplifiers (model 11-5407-58) to provide patient isolation and then into DC Gould universal amplifiers (model 13-4615-58). The amplifiers for the monophasic action potential and electrogram were set to give an output of 1 V for 40 mV input with a frequency response of 300 Hz. The signals were displayed on a Simonsen and Weel monitor (Model MTS 102). The electrocardiogram was amplified. A Gould instruments brush 220 pen recorder was used for hard copy recordings of the electrogram, monophasic action potential, and routine electrocardiogram at a paper speed of 1, 5, 25 or 125 mm/s as appropriate. The monophasic action potential and electrogram recordings were calibrated with a direct current millivolt source (Time Electronics model 4045).

PROCEDURE

All patients had had a coronary arteriogram with left ventricular angiogram via the right femoral artery by the Judkins technique on a previous occasion. This was repeated immediately before angioplasty with an Advanced Cardiovascular Systems incorporated French 9 shaft tip guiding catheter. After the immediate pre-angioplasty coronary arteriogram, a monophasic action potential catheter was inserted via the right femoral vein and positioned on the right ventricular septum in an area that would be expected to be supplied at least in part by the artery undergoing angioplasty.

The angioplasty balloon catheter (usually a Simpson ultra-low profile balloon catheter, Advanced Cardiovascular Systems, Incorporated), and guide wire (usually a 0·014 inch flexible steerable wire, USCI, CR Bard Incorporated) were advanced into the target artery. Once the guide wire had crossed the lesion, an electrogram signal was obtained from the wire. The dilatation catheter was then advanced across the stenosis. Recordings were then made of the electrogram, monophasic action potential, and routine electrocardiogram during successive balloon inflations. Up to four successive balloon inflations were carried out for 60 seconds with 2–5 minutes interval between them during which time the catheter and guide wire remained in position. Atrial pacing was not used routinely but was established when necessary (two patients).

STATISTICAL ANALYSIS

ST segment shift in the electrogram and electrocardiogram was measured at 60 ms after the J point. These data were displayed and presented in millimetres rather than millivolts as these represent the changes normally seen by the operator and used to monitor the procedure. A millivolt scale is included.

The QT interval was measured only in those records where the end of the T wave could be clearly defined. The QT measurements are presented (uncorrected for rate) with respective RR intervals.

The duration of the monophasic action potential was measured at 90% repolarisation by drawing a tangent to the steepest part of the slope. These data were normalised to take account of differences in heart rate between patients.

The angiographic result was assessed as good or moderate by visual inspection at the time of the procedure. The result was classified as good when the residual stenosis was < 20% and moderate when the residual stenosis was between 20% and 50%.

Results

ST SEGMENT

An ST segment shift in the epicardial electrogram was invariably upwards—that is ST elevation. In the electrocardiogram, ST shift was either up or down—that is elevation or depression depending upon the orientation of the lead position.

Most patients undergoing angioplasty of the left anterior descending or circumflex coronary arteries showed ST changes in the epicardial electrogram during the procedure (fig 1). These ST changes were usually more conspicuous than in the routine electrocardiogram and sometimes spectacular. In two of 13 patients ST changes were consistently seen in the electrogram when no ST shift occurred in the electrocardiogram. In two of the 13 patients ST changes developed in the electrocardiogram in the absence of either any change (patient 6) or minimal change (patient 13) in the electrogram. The elec-

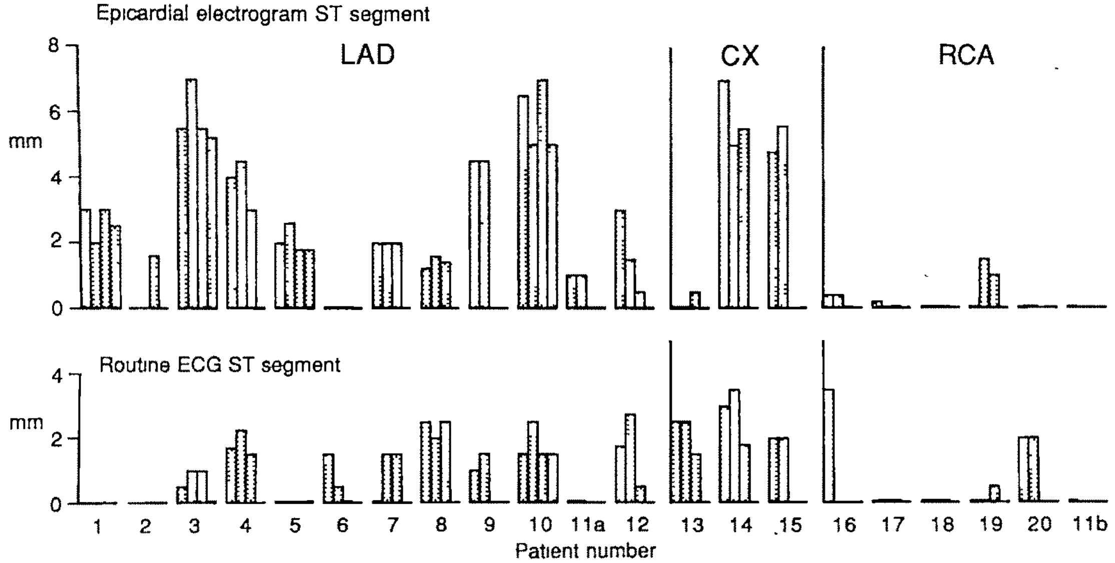


Fig 1 *Histogram showing ST segment shift in millimetres in the epicardial electrogram (top) and routine electrocardiogram (bottom) after 60 seconds of balloon occlusion (up to four balloon occlusions per patient) of the left anterior descending (LAD) circumflex (Cx), and right coronary artery (RCA) during angioplasty. The ST segment shift in the epicardial electrogram was invariably upwards. In the electrocardiogram ST shift was either up or down depending on the orientation of the lead position.*

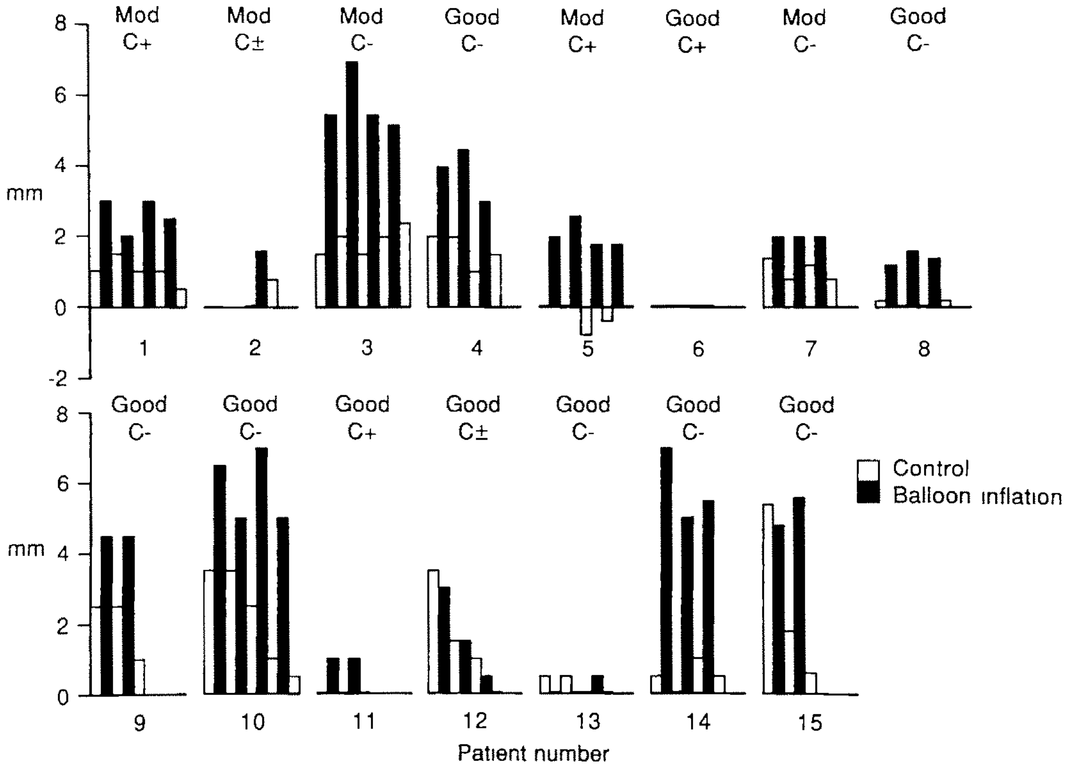


Fig 2 *Histogram showing ST segment elevation in millimetres in the epicardial electrogram during up to four balloon occlusions of the left anterior descending (patients 1–12) and the circumflex (patients 13–15) coronary artery during angioplasty. Control values were recorded with the deflated balloon in position across the lesion after 60 seconds' balloon inflation. The result of the procedure is indicated as either good or moderate. Angiographic evidence of the development of collaterals in the area of myocardium served by the vessel undergoing angioplasty is noted: C+, present; C−, absent.*

trogram recorded from the right coronary artery (six patients) yielded a signal of very low amplitude with a poorly defined T wave and showed either small or no changes in the ST segment during angioplasty.

The ST elevation in the electrogram developed during insertion of the catheter before inflation of the balloon in 11 of the 15 patients undergoing angioplasty of the left anterior descending artery or circumflex coronary artery (fig 2). Figure 3a shows an example. In eight of the 11 patients showing pre-inflation ST elevation, the ST shift lessened after successive inflations. Figure 2 shows that 11 of 15 pre-first inflation ST measurements (that is balloon in position before inflation) already show ST elevation. The progressive development of ST elevation after the catheter was positioned across the stenosis before inflation is illustrated in the slow playout in fig 3a. Two successive balloon inflations of the same lesion are shown in figs 3a and 3b, which show the progressive development of ST elevation during inflation and lessening of the ST elevation after balloon deflation. There is a striking contrast between the ST elevation in the electrogram and the absence of ST shift in the electrocardiogram.

The electrocardiogram lead selected for monitoring during the procedure that we studied was the one we considered most likely to show changes according to the site of the vessel undergoing angioplasty (table 1). In five patients who showed ST elevation in the electrogram the standard limb leads and V5 were recorded during the last 10 seconds of balloon inflation. No ST changes were evident in any of the leads.

RECORDINGS OF MONOPHASIC ACTION POTENTIAL

Monophasic action potentials were recorded during 45 balloon occlusions in 19 patients (left anterior descending artery, 25 observations in 10 patients; circumflex artery, eight observations in three patients; right coronary artery, 12 observations in six patients). In the patients undergoing angioplasty for lesions of the circumflex coronary artery the duration of the monophasic action potential duration showed

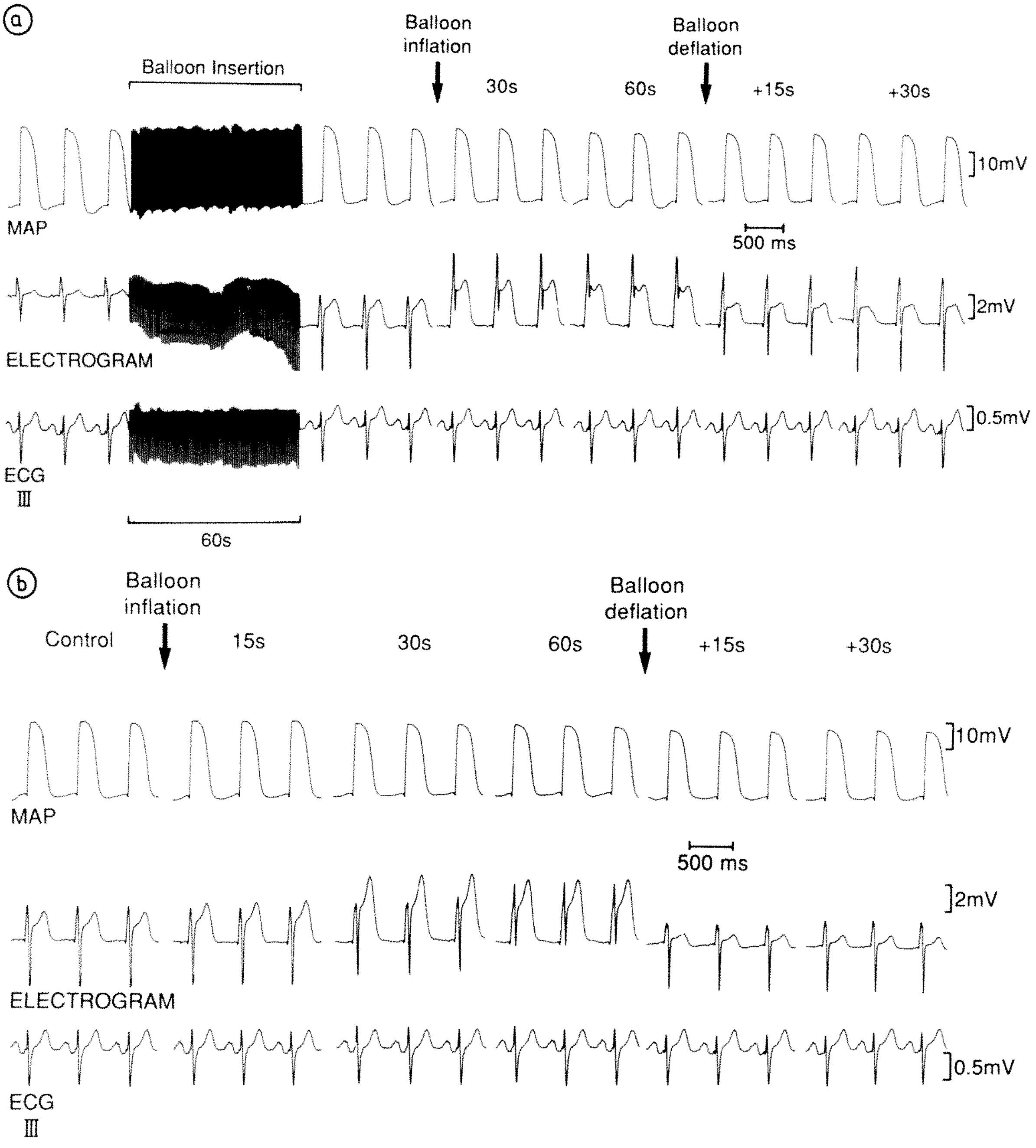


Fig 3 *(a) Monophasic action potential (MAP), electrogram, and routine electrocardiogram (lead III) in a patient undergoing angioplasty of the circumflex coronary artery. During the 60 seconds after insertion of the deflated balloon there was progressive ST elevation in the electrogram on the slow playout with little change in the electrocardiogram. ST elevation increased in the electrogram during the 60 second period of balloon inflation and decreased after deflation although some elevation persisted. The electrocardiogram remained unchanged throughout. No changes were seen in monophasic action potential (MAP) duration. (b) A second balloon inflation on the same patient performed after three minutes' rest. The ST elevation in the electrogram again increased but this time it returned to the isoelectric line (with the balloon still in position) after deflation. The ST segment in the electrocardiogram (ECG) and monophasic action potential (MAP) duration were unchanged throughout.*

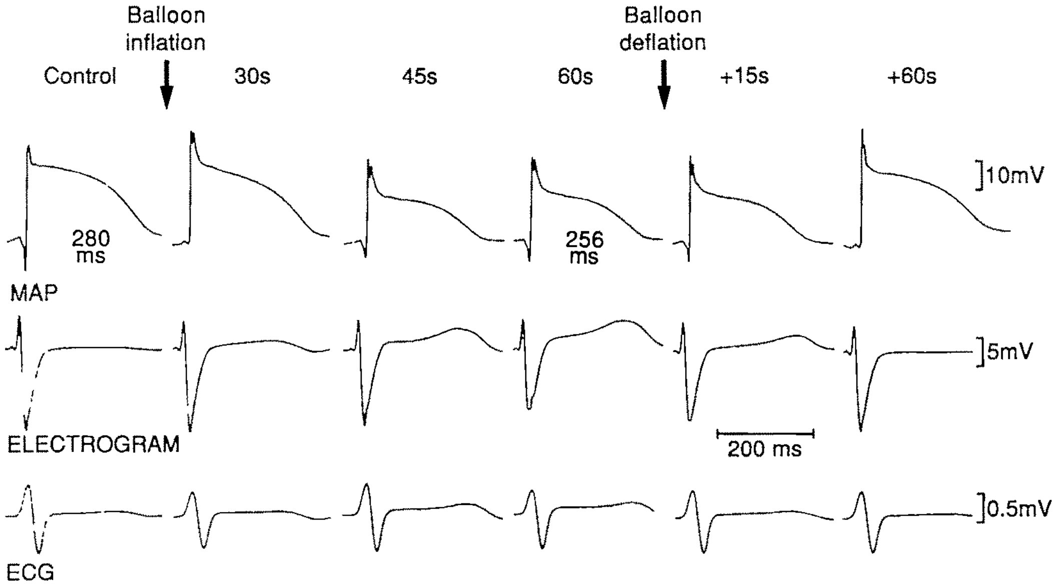


Fig 4 *Monophasic action potential (MAP), electrogram, and electrocardiogram (V5) of patient undergoing angioplasty of the left anterior descending coronary artery. During the 60 seconds of balloon inflation ST elevation developed in the electrogram and to a lesser extent in the electrocardiogram accompanied by shortening of monophasic action potential duration.*

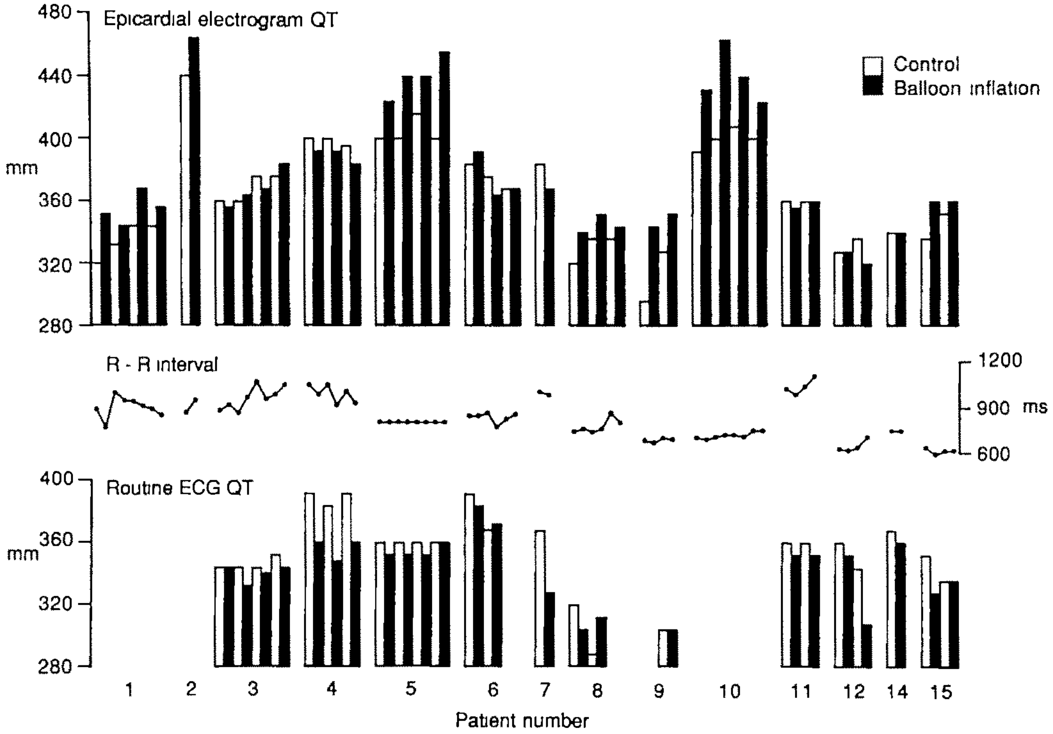


Fig 5 *QT interval in the epicardial electrogram (top) and routine electrocardiogram (ECG) (bottom) in patients undergoing angioplasty of the left anterior descending (patients 1–12) and circumflex (patients 13–15) coronary arteries. Values were recorded with the deflated balloon in position across the lesion (control) and at 60 seconds balloon inflation. The respective RR intervals are shown in the centre panel.*

Table 2 *Change in QT interval in the electrogram and electrocardiogram (ECG) during angioplasty at 60 s balloon inflation compared with control in two groups*

Δ RR interval between control and 60 s balloon occlusion	*QT interval change*	*Electrogram*	*ECG*
< 20 ms	Prolongation	14	1
	No change	2	3
	Shortening	1	8
		n=17/36	n=12/24
< 40 ms	Prolongation	18	1
	No change	3	4
	Shortening	4	10
		n=25/36	n=15/24

Occasions where the RR interval changed by < 20 ms (top) and by < 40 ms (bottom) are presented. Thirty six patients had measurable QT intervals in the electrogram whereas only in 24 was QT measurable in the electrocardiogram Of the 36 patients only 17 showed RR interval changes of < 20 ms during the procedure of which only 12 had measurable QT changes in the electrocardiogram. A further eight patients showed changes in the RR interval of between 20 and 40 ms of whom only three had measurable QT intervals in the electrocardiogram.

no change, with the mean normalised monophasic action potential duration at 60 seconds inflation being 100·4 (1·2) % of control. In patients undergoing angioplasty of the right coronary artery only minimal changes in monophasic action potential duration were seen, the mean value at 60 seconds occlusion being 99·6 (1·5) % of control. In the patients undergoing angioplasty of the left anterior descending coronary artery, 19 of the total of 25 inflations showed shortening of the monophasic action potential of < 5%, five showed shortening of between 5 and 10%, and one showed a shortening of 16·4%.

Figure 4 shows an example of shortening of the monophasic action potential duration associated with ST elevation in the electrogram.

QT INTERVAL

Figure 5 shows the QT interval of the electrogram and routine electrocardiogram. We were able to measure the QT interval satisfactorily in 36 balloon inflations in the electrogram and in 24 of these occasions in the electrocardiogram. In the one patient in this group who was paced (patient 5) the QT interval in the electrogram consistently lengthened during successive balloon occlusions whereas in the electrocardiogram there was progressive shortening of the QT interval. A similar disparity was seen between the QT interval in the electrogram and electrocardiogram on the occasions when only minimal changes in cycle length occurred (table 2).

Table 3 *ST segment elevation in the epicardial electrogram (mm) with the deflated balloon in situ before dilatation (left of each arrow) and at the end of successive inflations (right of each arrow) still with the deflated balloon in situ*

Good result		*Moderate result*	
C+	*C−*	*C+*	*C−*
0→0	2→1·5	1→0 5	1·5→2 4
0→0	0 2→0 2	0→0·8	1·4→0 8
3·5→0	2·5→1	0→0	
	3 5→0·5		
	0 5→0		
	0 5→0 5		
	5·4→0 6		

C+, angiographic evidence of good collateral supply,
C−, no angiographic evidence of collateral supply.

Table 4 *ST shift (mm) in the electrogram (EG) and electrocardiogram (ECG) at 60 s balloon inflation during antioplasty (mean (SD))*

	Collaterals		*No collaterals*	
Balloon inflation	*ST shift (EG)*	*ST shift (ECG)*	*ST shift (EG)*	*ST shift (ECG)*
First	1 5 (1 3)	0 8 (0·9)	3 9 (2 4)	1·6 (1·0)
	(n=4)		(n=9)	
Second	1·4 (0·9)	0·7 (1 4)	3 9 (2 2)	2 1 (0·7)
	(n=4)		(n=9)	
Third	0 8 (0·9)	0·2 (0·3)	3·6 (2·4)	1·6 (0 5)
	(n=3)		(n=7)	
All	1·3 (1 0)	0·6 (1 0)	3·8 (2·3)	1·8 (0 8)
	(n=11)		(n=25)	

Data are given separately for first, second, third, and all inflations and subdivided into those patients with angiographic evidence of collaterals and those without.

CORRELATION WITH ANGIOGRAPHIC EVIDENCE OF THE DEVELOPMENT OF COLLATERALS

Figure 2 and table 1 show the angiographic evidence of collateral blood flow to the area of myocardium normally supplied by the vessel undergoing angioplasty. Six of the 15 patients showed clear evidence of the development of collaterals to the compromised area of myocardium. The ST segment elevation in both the electrogram and the electrocardiogram was considerably less pronounced in those patients with evidence of the development of collaterals than in those without. The size of the change in the electrogram was twice that in the electrocardiogram (table 4). Furthermore, the initial ST elevation in the electrogram was less pronounced when the deflated balloon was in place across the stenosis before the first balloon inflation in those patients with well developed collaterals than in those without (table 3).

CORRELATION WITH THE RESULT OF THE PROCEDURE

Ten of the 15 patients undergoing angiography of the left system were classified as having a good angiographic result and five as having a moderate result (table 2, fig 2). Table 4 shows that patients with a high initial ST elevation in whom a good result was

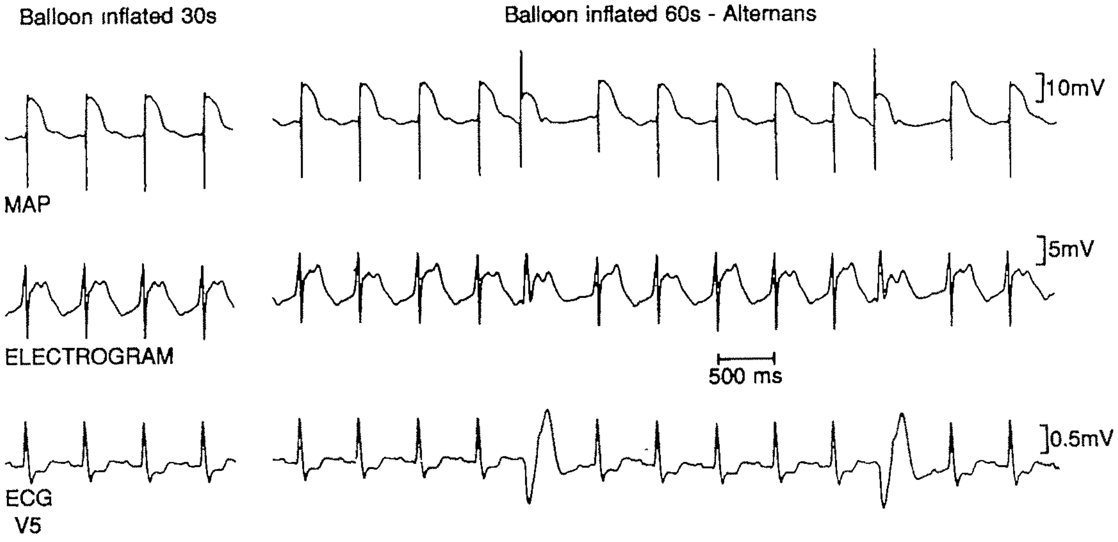


Fig 6 *Patient undergoing angioplasty of the left anterior descending coronary artery. At 60 seconds of balloon occlusion ST/T alternans was seen in the electrogram which was not evident in the electrocardiogram (ECG). Ventricular extrasystoles developed and became frequent at this time. "Humps" at the end of repolarisation in the monophasic action potential (MAP) signal may be early after-depolarisations.*

achieved tended to show a substantial fall in this elevation by the end of the procedure.

ALTERNANS

One patient (case 10) undergoing angioplasty of the left anterior descending coronary artery developed T wave alternans which was obvious on the electrogram but not apparent in the electrocardiogram (fig 6). The alternans developed after 45 seconds of balloon occlusion and ceased after about 10 seconds of balloon deflation. During this period there were frequent ventricular extrasystoles.

Discussion

We found that ST changes on the guide wire electrogram during angioplasty are more obvious than those in the electrocardiogram and more sensitive to changes occurring in the area of myocardium being reperfused. This is to be expected in view of the wider angle subtended at the recording site for the electrogram, which is only a few millimetres away from the myocardium whereas the electrocardiogram electrode is more remote. However, this is not always the case and sometimes the reverse occurs. A possible explanation may be that solid angle theory applies to a point source whereas the guide wire is a continuum of several centimetres which may overlie areas of well perfused myocardium. This could be especially so when there is a good development of collaterals. A further possibility is that the guide wire may overlie scar tissue that is less likely to respond electrically. This suggestion was made by Friedman *et al* to explain the lack of any discernible shift in the ST segment in the four patients they studied undergoing angioplasty for distal right coronary artery disease.[11] We also saw little change in our six patients undergoing angioplasty of the right coronary artery, which suggests that it is unlikely that nearly all patients undergoing angioplasty for right vessel coronary artery disease have scar tissue close to the guide wire; however, only two of the patients under study for the left system did not show ST changes. We therefore suggest an alternative explanation: that the fat separating the right coronary artery from the myocardium may act as an insulator. Cancellation is an alternative possibility. Whatever model of the electrocardiographic waveform is considered, the waveform is essentially the algebraic sum of multiple potential differences throughout the myocardium. Owing to the spatial orientation of the conduction sequence across the ventricles the recording electrode will usually record several positive and negative potential differences. If the algebraic sum of these is zero during the inscription of the ST segment then the isoelectric line will not shift. We consider this unlikely because we often found that an extrasystole with its different spatial orientation to the wire had no influence on the electrogram recorded from the right coronary artery. If cancellation were a major factor then the altered vector would be expected to modify significantly the configuration of the electrogram.

Measurements of the QT interval in the electrogram showed little correlation with the electrocardiogram; this is not unexpected because the angles subtended at the respective electrode recording sites are very different. Some of these differences may be due to the known patchy nature of ischaemia and localised differences in collateral response. It is also difficult to analyse the small changes in QT interval because the heart rate in the patients, who were not paced, was variable. We agree that rate correction of the QT interval is inappropriate and may be misleading.[13–15] Bazett's correction,[16] and other formulas[17] are intended to compensate for physiological variation in heart rate. However, the relation between QT interval and heart rate depends not only on the instantaneous interval between beats but also upon the variation in the heart rate during the preceding 2–3 minutes.[15] In addition it is affected by other factors such as autonomic tone.[18] The QT interval is known to increase in ischaemia owing to increased dispersion of action potentials. In most patients in whom the heart rate was steady during the sequence of balloon occlusion the QT interval was prolonged although this was not inevitably the case. This again is possibly because of differences in local microcirculatory tone.

Recordings of monophasic action potential correlated with the repolarisation phase of the underlying transmembrane potential.[19–21] Changes in action potential duration are a sensitive index of the early electrophysiological changes produced by regional myocardial ischaemia. The monophasic action potential characteristically records electrical events occurring within a radius of 2–3 mm.[21 22] This localised nature of the recordings is one of the main advantages of monophasic action potential recordings over electrograms and electrocardiograms. Though the monophasic action potential recording was close to the area of intervention in most patients the monophasic action potential did not register any ischaemic change. This indicates the limited extent of the ischaemia during the 60 second angioplasty occlusion.

The localised zone of initial ischaemia also accords with the relatively greater ST shift seen in the electrogram than in the electrocardiogram. Angiographic evidence of the development of collaterals seemed to influence the ST segment in the electrogram.

When the deflated balloon was positioned across the stenosis ST elevation was often seen in the electrogram in those patients without evidence of the development of collaterals, but there was little or no ST elevation when collaterals were present, except in one patient. The presence of collaterals seemed to lessen the degree of ST elevation in the electrogram associated with balloon inflation. After angioplasty when the deflated balloon was still in position across the stenosis we often saw residual ST elevation in patients with no evidence of collaterals but it was usually only slight when collaterals were present.

Undoubtedly, the relative sizes of the deflated balloon and the patent diameter of the stenotic areas will have influenced the above results. After angioplasty these relative sizes will be more disparate in patients with a good result than in patients with a moderate result. Residual ST elevation was less pronounced in patients with a good result than in patients with a moderate result (table 3).

In one patient T wave alternans developed that was obvious in the electrogram but not seen in the electrocardiogram or monophasic action potential (fig 6); this shows that alternans can be a local phenomenon and can be silent in the electrocardiogram. It is reasonable to assume that the alternans of the T wave in this patient reflects alternating local differences in action potential duration. Alternans has been shown to be arrhythmogenic in the presence of ischaemia by various mechanisms including triggered activity and re-entry.[23 24] In our patient ventricular extrasystoles were common when alternans was present but not in its absence. The truly local nature of this alternans is highlighted by the persistence of the sequence of changes in T wave amplitude when ventricular extrasystoles intrude and the activation vector is altered.

We conclude that in patients undergoing angioplasty the electrophysiological changes occurring within the myocardium during a 60 second balloon inflation sequence are usually very localised. These changes are thereby more obvious in an electrogram recorded directly from the area than in the more distantly placed electrocardiogram. The signals obtained from the right coronary artery are of low voltage and do not yield a useful record unlike those from the left system. The usual absence of changes in the monophasic action potential when the recording electrode was in the area supplied by the vessel undergoing angioplasty further emphasises the very local nature of the ischaemic changes. The local nature of the electrogram signal is further supported by the presence in one patient of electrical alternans that was silent in the electrocardiogram and monophasic action potential. The QT interval in the electrogram did not correlate with the QT interval in the electrocardiogram. The resting ST segment in the electrogram and the shift associated with balloon inflation seemed to be influenced by angiographic evidence of collaterals. Finally, the intracoronary electrogram in the left system provides useful access for the electrophysiological recording of early ischaemic events, which may be useful in certain patients during angioplasty and may have a research application.

We thank Paula Cupitt and the staff of the cardiac catheterisation laboratory for their help and the Middlesex Hospital Trustees for financial support (PT).

References

1 Burchell HB. Did Einthoven invent a string galvanometer? *Br Heart J* 1987;57:190–3.

2 Krikler DM. Electrocardiography then and now: where next? *Br Heart J* 1987;57:113–7.

3 Lazzara R, El-Sherif M, Scherlag BJ. Early and late effects of coronary artery occlusion on canine Purkinje fibres. *Circ Res* 1974;35:391–9.

4 Holland RP, Arnsdorf MF. Solid angle theory and the electrocardiogram: physiologic and quantitative interpretations. *Prog Cardiovasc Dis* 1977;19:431–57.

5 Spach MS, Barr RC, Lanning CF, Tucek PC. Origin of the body surface QRS and T wave potentials from epicardial potential distributions in the intact chimpanzee. *Circulation* 1976;55:268–78.

6 Taggart P, Sutton P, Runnalls M, *et al.* Use of monophasic action potential recordings during routine coronary artery bypass surgery as an index of localised myocardial ischaemia. *Lancet* 1986;i:1462–4.

7 Franz MR, Flaherty JT, Platia EV, Bulkley BH, Weisfeldt ML. Localisation of regional myocardial ischaemia by recording monophasic action potentials. *Circulation* 1984;69:593–604.

8 Donaldson RM, Taggart P, Bennett JG, Rickards AF. Study of electrophysiological ischaemic events during coronary angioplasty. *Texas Heart J* 1984;11:24–30.

9 Taggart P, Sutton PMI, Hayward R, Emanuel RW, Swanton RH. Epicardial electrogram during angioplasty [Abstract]. *Br Heart J* 1988;59:133–4.

10 Meier B, Rutishauser W. Coronary pacing during percutaneous transluminal coronary angioplasty. *Circulation* 1985;71:557–61.

11 Friedman PL, Shook TL, Kirshenbaum JM, Selwyn AP, Ganz P. Value of intracoronary electrocardiogram to monitor myocardial ischaemia during percutaneous transluminal coronary angioplasty. *Circulation* 1986;74:330–9.

12 Taggart P, Sutton PMI, John R, Hayward R, Runnals ME, Swanton RH. Epicardial electrogram during successive balloon occlusion during percutaneous transluminal coronary angioplasty [Abstract]. *Br Heart J* 1989;61:84.

13 Ward DE, Camm AJ. Q-T interval syndromes. *Lancet* 1988;ii:47–8.

14 Lau CP, Freedman AR, Fleming S, Malik M, Camm AJ, Ward DE. Hysteresis of the ventricular paced QT interval in response to abrupt changes in pacing rate. *Cardiovasc Res* 1988;22:67–72.

15 Seed WA, Noble MIM, Oldershaw P, *et al.* Relation of human cardiac action potential duration to the interval between beats: implications for the validity of rate corrected QT interval (QTc). *Br Heart J* 1987;57:32–7.

16 Bazett HC. An analysis of the time relationship of electrocardiograms. *Heart* 1920;7:353–70.

17 Sarma JSM, Venkataraman K, Samant DR, Gadgil UG. Effect of propranolol on the QT intervals of normal individuals during exercise: a new method for studying interventions. *Br Heart J* 1988;60:434–9.

18 Browne KP, Zipes DP, Heger JJ, Prystowsky EN. Influence of the autonomic nervous system on the QT interval in man. *Am J Cardiol* 1982;50:1099–103.

19 Hoffman BF, Cranefield PF, Lepeschkin D, Surawicz B, Herlich HC. Comparison of cardiac monophasic action potentials recorded by intracellular and suction electrodes. *Am J Physiol* 1959;196:1297–301.

20 Franz MR, Burkhoff D, Spurgeon H, Weisfeldt ML, Lakatta EG. In vitro validation of a new cardiac catheter technique for recording monophasic action potentials. *Eur Heart J* 1986;7:34–41.

21 Blake K, Clusin WT, Franz MR, Smith NA. Mechanism of depolarization in the ischaemic dog heart: discrepancy between T-Q potentials and potassium accumulation. *J Physiol (Lond)* 1988;397:307–30.

22 Levine JH, Guarnieri T, Kadish AH, White RI, Calkins H, Kan JS. Myocardial repolarisation changes in patients undergoing balloon valvuloplasty: evidence of contraction-excitation feedback in man. *Circulation* 1988;77:72–7.

23 Lab MJ. Contraction excitation feedback in myocardium: physiological basis and clinical relevance. *Circ Res* 1982;50:757–66.

24 Dilly SG, Lab MJ. Electrophysiological alternans and restitution during acute regional ischaemia in myocardium of anaesthetized pig. *J Physiol (Lond)* 1988;402:315–33.

Br Heart J 1989;62:353–60

A study of nerves containing peptides in the pulmonary vasculature of healthy infants and children and of those with pulmonary hypertension

KIM M ALLEN, JOHN WHARTON,* JULIA M POLAK,* SHEILA G HAWORTH
*From the Institute of Child Health and *Royal Postgraduate Medical School, London*

SUMMARY Nerves containing peptides that supply the human intrapulmonary vasculature were studied in 21 controls aged one month to 24 years and in 13 patients with pulmonary hypertension aged 11 days to eight years. An indirect immunofluorescence technique was used to study the distribution and relative density of nerve fibres containing the general neuronal marker, protein gene product 9·5; tyrosine hydroxylase; synaptophysin; neuropeptide tyrosine; vasoactive intestinal polypeptide; substance P, somatostatin; and calcitonin gene related peptide. At all ages in normal and hypertensive lungs neuropeptide tyrosine was the predominant neuropeptide associated with the pulmonary vascular nerves. In normal lungs the relative density of nerve fibres increased during childhood only in the arteries of the respiratory unit. Pulmonary hypertension was associated with the premature innervation of these arteries during the first year of life.

Innervation of small, abnormally thick-walled pre-capillary vessels by predominantly vasoconstrictor nerves may help to explain the susceptibility of infants to pulmonary hypertensive crises.

There is no reliable effective medical treatment for pulmonary hypertension. Children with potentially reversible pulmonary vascular disease can die after a technically successful intracardiac repair because of the development of pulmonary hypertensive crises that become intractable to all forms of treatment. Pharmacolological management of pulmonary hypertension might be improved by understanding how the pulmonary vasculature is innervated in such a lung.

During normal development the wall structure of the entire pulmonary arterial tree is remodelled. Connective tissue is deposited and medial smooth muscle cells differentiate, acquiring a contractile rather than a synthetic phenotype.[1] The concentration of contractile myofilaments increases and the type of cytoskeletal proteins change.[2] In children with pulmonary hypertensive congenital heart disease these changes are accelerated or abnormal.[3] The relation between remodelling of the pulmonary arteries and pulmonary innervation in the human lung is unclear. In the normal immature pig lung differentiation of smooth muscle cells is accompanied by an increase in the density of presumed sympathetic nerves.[4] Experimental studies showed trophic interactions between sympathetic nerves and vascular smooth muscle cells.[5]

The adult human pulmonary vasculature is innervated by noradrenergic and cholinergic nerves[6 7] but these nerves also contain other putative transmitters, including several vasoactive peptides, which may have a regulatory role in the pulmonary circulation. Examples of such peptides identified in mammalian pulmonary nerves include vasoactive intestinal polypeptide[8] (predominantly in parasympathetic nerve fibres), substance P and the neurokinins[9] and calcitonin gene related peptide[10] (all present in sensory nerve fibres), and neuropeptide tyrosine[11] (in sympathetic fibres) as recently reviewed by Lundberg *et al.*[12]

We used immunocytochemical techniques to examine the innervation of the pulmonary vasculature in the normal and pulmonary hypertensive human lung. The overall pattern of innervation was studied with an antiserum to general neuronal cytoplasmic marker, protein gene product 9·5. Specific subpopulations of nerve fibres were identified by antibodies to neuropeptides and to the enzyme tyrosine hydroxylase which synthesises catecholamines.

Requests for reprints to Professor Sheila G Haworth, Institute of Child Health, 30 Guilford Street, London WC1N 1EH.

Accepted for publication 27 July 1989

Patients and methods

The innervation of the intrapulmonary arteries and veins and the bronchial arteries was examined at necropsy in 18 children and three adults without cardiopulmonary disease and in 13 children who had pulmonary hypertension (table 1). In 11 children, pulmonary hypertension was caused by congenital heart disease and two had primary idiopathic pulmonary hypertension of the newborn. Lung tissue was obtained less than 24 hours after death. Blocks of tissue (1 cm² × 0·5 cm) were dissected out from the hilum to the periphery to include airways and their associated arteries so that elastic, large and small muscular arteries were samples in addition to the alveolar region of the lung. Tissue blocks were fixed overnight (9–12 hours) at 4°C in a modified Bouin's solution.[4] After the tissue was rinsed in several changes of phosphate buffered saline (0·1 mol/l, pH 7·2) containing 15% (w/v) sucrose and 0·1% sodium azide, cryostat blocks were prepared and stored in liquid nitrogen. Transverse cryostat sections (15 μm thick) were collected on glass slides coated with poly-L-lysine and allowed to dry for an hour at room temperature. Before immunostaining by the indirect immunofluorescence technique, sections were immersed in phosphate buffered saline containing 0·2% Triton X-100 for an hour at room temperature, rinsed in phosphate buffered saline, then counterstained with pontamine sky blue (BDH Chemicals) to reduce background autofluorescence.

The innervation was shown with primary antisera[13] to general neuronal markers and specific neuropeptides (table 2). The general neuronal cytoplasmic marker protein gene product 9·5 occurs in all peripheral nerves and in all regions of the neurone.[14] Synaptophysin is a membrane protein specifically associated with small secretory vesicles thought to contain the classic neurotransmitters in nerve terminals.[15] Antisera to both the sequences flanking the active and carboxy terminals of the neuropeptide tyrosine precursor molecule were used and have been shown to have an identical distribution pattern.[16] Tachykinin-like immunoreactivity was shown with antibodies raised to substance P but which cross react with the neurokinins A and B. Sections were incubated with fluorescein isothiocyanate-conjugated sheep anti-rabbit IgG (Wellcome Diagnostics) for an hour at room temperature. After a further rinse in phosphate buffered saline, sections were mounted in phosphate buffered saline/glycerol. Controls included the application of pre-immune serum as first layer and diluted primary antisera preabsorbed with peptide (1–20 × 10^{-6} mol/l). Tissue sections were examined by a fluorescence microscope (Olympus Vanox AH-2).

Table 1 *Data on 21 controls and 13 infants and children with pulmonary hypertension*

Controls		*Pulmonary hypertension*	
Age	*No*	*Age*	*No*
1 mnth	3	11 days	1
2 mnths	2	2 mnths	3
3 mnths	2	6–10 mnths	2
4 mnths	2	1–1·5 yrs	3
9–10 mnths	2	2·5–3 5 yrs	3
1–1·5 yrs	3	8 yrs	1
2·5–3·5 yr	4		
Adult	3		

We checked that the pulmonary vasculature in those who died without cardiopulmonary disease was indeed normal. Therefore blocks of tissue from areas of the lung adjacent to those used for the immunofluorescence study were prepared for light microscopical examination after staining with haematoxylin and eosin and with Miller's elastin stain counterstained with van Geison's stain. The percentage arterial medial thickness (2 × medial thickness divided by external diameter) in arteries of different sizes and the external diameter of arteries within the respiratory unit was determined and the findings were compared with those of a previous extensive light microscopical study of normal pulmonary arterial development.[17]

Results

FEATURES COMMON TO ALL THOSE EXAMINED AT ALL AGES

Intrapulmonary arteries

The distribution of nerves accompanying the pulmonary arteries was assessed by the general neuronal marker, protein gene product 9·5. Immunoreactivity was seen in nerve trunks and single varicose fibres or fascicles (figs 1 and 2a and b). Nerve trunks containing preterminal axons were found in the mid-outer adventitia of arteries proximal to the respiratory unit.

Table 2 *Antisera used to test for peptides in nerves*

Antiserum to:	*Code*	*Dilution*
General neuronal markers:		
Protein gene product 9 5	1648	1:600
Synaptophysin	1623	1:800
Specific neuropeptide subtypes:		
Neuropeptide tyrosine (NPY)	1086	1:400
C-flanking peptide of NPY	1411	1:600
Vasoactive intestinal peptide	652	1:2000
Somatostatin	1082	1:400
Substance P	910	1:500
Calcitonin gene related peptide	1208	1:200
Atrial natriuretic peptide (1–28)	1607	1:200
Tyrosine hydroxylase	*1731*	*1:100*

(See [15] for further characterisation of these antisera.)

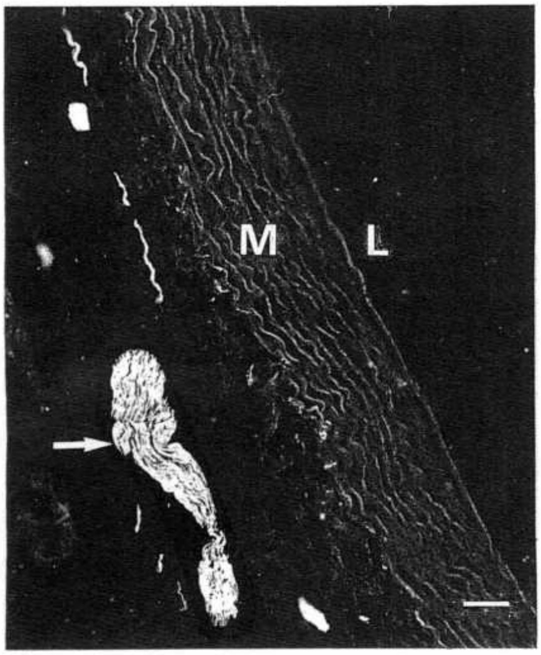


Fig 1 *Photomicrograph of transverse section of an elastic intrapulmonary artery showing nerve trunks in the adventitia (arrow) that are immunoreactive for protein gene product 9·5. L, lumen; M, media. Scale bar = 50 μm.*

They ran mainly parallel to the vessels and decreased in size and number from the hilum. Single, mainly varicose, nerve fibres and fascicles occurred predominantly at the adventitial-medial border and in the inner part of the adventitia in all arteries. No nerve fibres were seen within the media of small muscular arteries and only rarely penetrated into the outermost lamellar unit of elastic arteries. Nerve fibres were never seen accompanying arteries within the alveolar wall.

Most of the nerve fibres immunostained for protein gene product 9·5 seemed to be sympathetic in origin, showing both tyrosine hydroxylase (fig 2a and b) and neuropeptide tyrosine immunoreactivity (fig 3). Subpopulations of nerves showing immunoreactivity for other neuropeptides were far less common, fibres immunostained for vasoactive intestinal peptide being the most abundant of these. Immunostaining for vasoactive intestinal peptide was localised in fine, sparsely distributed varicose fibres, most commonly associated with small muscular arteries immediately proximal to the respiratory unit (fig 4). These nerves were occasionally seen with elastic and respiratory unit arteries. Varicose fibres that were immunoreactive for calcitonin gene related peptide were common in the nerve trunks but not elsewhere (fig 5). Somatostain-like and tachykinin-like immunoreactive fibres were rare in all types of artery.

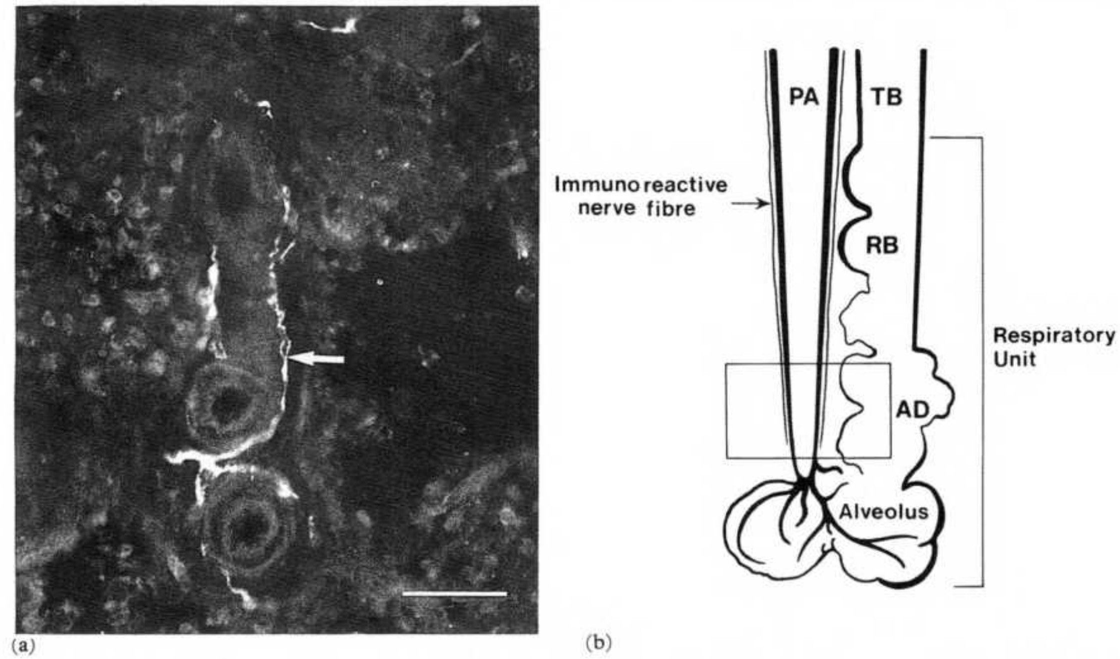


Fig 2 *(a) Tyrosine hydroxylase immunoreactive perivascular nerve fibres (arrow) at the adventitial-medial border of an alveolar duct artery in a child aged two and a half. Scale bar = 50 μm. (b) Diagram of terminal bronchiolus (TB) and airways of respiratory unit accompanied by an innervated pulmonary artery (PA). RB, respiratory bronchiolus; AD, alveolar duct. Square indicates area shown in (a).*

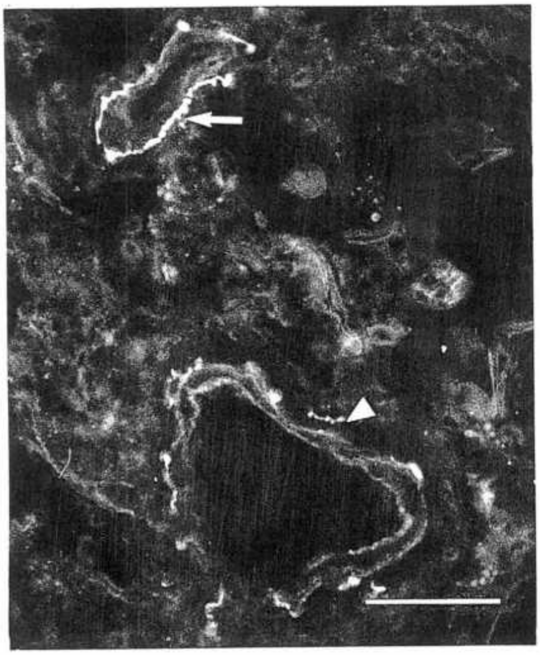


Fig 3 *Photomicrograph showing nerve fibres expressing neuropeptide tyrosine immunoreactivity accompanying an alveolar duct artery (arrow) and respiratory bronchiolar artery (arrowhead) in a three month old child. Scale bar = 50 µm.*

INTRAPULMONARY VEINS

The nerves immunostained for protein gene product 9·5 that accompanied the large proximal veins had a different distribution from that seen in proximal arteries; they formed a dense network throughout the adventitia (fig 6). Also these veins were more densely supplied with varicose nerve terminals, and nerve fibres could be found penetrating the muscle coat and extending to the subendothelium. There were more synaptophysin immunoreactive fibres present than in the arteries. In the wall of these veins and in the surrounding myocardial sheath most nerve fibres showed immunoreactivity for tyrosine hydroxylase and neuropeptide tyrosine. In some of the large proximal veins there was also a relatively dense subpopulation of somatostatin immunoreactive fibres, but fibres stained for other peptides were rare. Within the respiratory unit the veins were less densely innervated than the arteries. Atrial natriuretic peptide was localised to myocardial cells around hilar veins but was not detected elsewhere in the lung.

Bronchial arteries

Nerves accompanying the arteries of the systemic circulation were localised at the adventitial-medial border and like the pulmonary arteries were predominantly immunoreactive for neuropeptide tyrosine and tyrosine hydroxylase.

CHANGES IN NERVE SUBTYPE AND DISTRIBUTION RELATED TO AGE

In controls, changes in nerve distribution with age were confined to the arteries of the respiratory unit. In children aged 1–4 months, approximately one third of arteries accompanying alveolar ducts were not innervated but by the age of 2·5 almost all were innervated and in adulthood they were invariably innervated. While most nerves supplying arteries accompanying alveolar ducts were immunoreactive to protein gene product 9·5 and neuropeptide tyrosine, rare fibres containing vasoactive intestinal peptide were also found. Nerve fibres could not be shown accompanying veins lying in the alveolar region in individuals aged 1·5 years or less. In those aged 2·5 years, however, a small proportion of these veins were accompanied by protein gene product 9·5 and fibres that were immunostained for neuropeptide tyrosine.

FINDINGS IN PULMONARY HYPERTENSION

In the lungs of patients with pulmonary hypertension

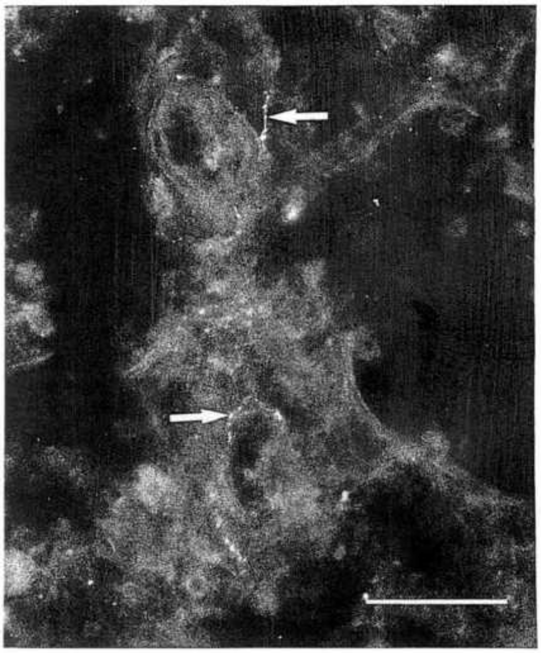


Fig 4 *Photomicrograph showing varicose nerve fibres (arrows) that were immunoreactive for vasoactive intestinal peptide accompanying small muscular arteries of a three month old child. Scale bar = 50 µm.*

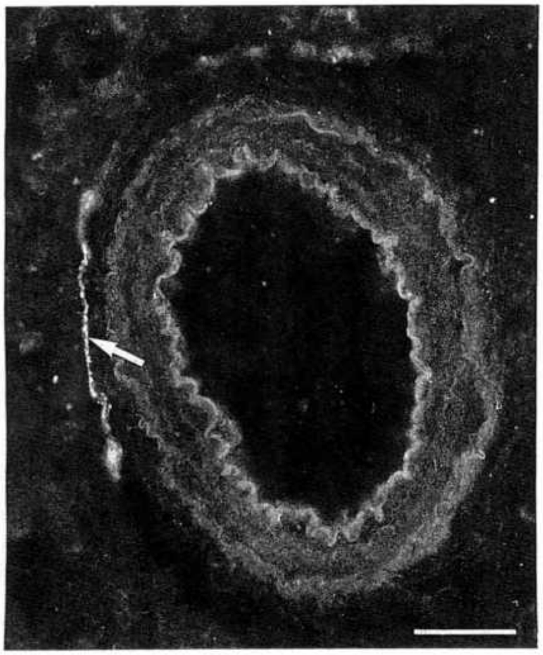


Fig 5 *Photomicrograph showing nerve fibres (arrow) that were immunoreactive for calcitonin gene related peptide associated with a muscular pre-acinar artery in the lung of a two and a half year old child. Scale bar = 50 μm.*

the density and distribution of the different subpopulations of nerve fibres within arteries and veins lying proximal to the respiratory unit were similar to that in the normal individuals at all ages. Within the respiratory unit, however, in all these patients alveolar duct arteries (fig 2a) were accompanied by protein gene product 9·5 (fig 7) and nerve fibres that were immunoreactive for neuropeptide tyrosine (fig 8), even in those who were only 11 days old. The two patients with idiopathic persistent pulmonary hypertension also showed extension of nerves into more distal veins than was normal for their age. We found no other differences in distribution or expression of peptide immunoreactivity.

Discussion

This study showed that the innervation of the human pulmonary vasculature increases during childhood. Many arteries and veins of the respiratory unit did not have any accompanying nerve fibres in children aged 1–4 months, but the proportion of innervated vessels increased with age. This increase was more pronounced in the arterial than in the venous bed. These findings contrast with those in the pig where the distribution of nerves was as extensive at birth as in mature animals and nerve density in all arteries increased with age.[4] These differences may be associated with the earlier extension of smooth muscle to more peripheral arteries and the faster differentiation of vascular smooth muscle cells in the pig.[1 18]

In the human lung, nerves supplying the large intrapulmonary arteries and veins differed in their distribution, because varicose nerve terminals were often seen penetrating the muscle coat in veins but not arteries. This may reflect a difference in the way in which the nerve stimulus is propagated in the two types of vessel. In the arteries, this may be due to diffusion of neurotransmitter across the vessel wall or to electrocoupling of the medial smooth muscle cells via gap junctions.[19 20] In the veins, however, the greater amount of connective tissue and fibroblasts may hinder such processes and help explain the more direct innervation of venous smooth muscle cells. Alternatively, the scarcity of nerves in the media of arteries may be related to the higher intra-arterial pressure because pressure-induced degeneration of somatic nerves has been shown in the sheep carotid artery.[20]

Most perivascular nerves were presumed to be sympathetic in origin in both normal and abnormal tissue at all ages. They expressed both tyrosine

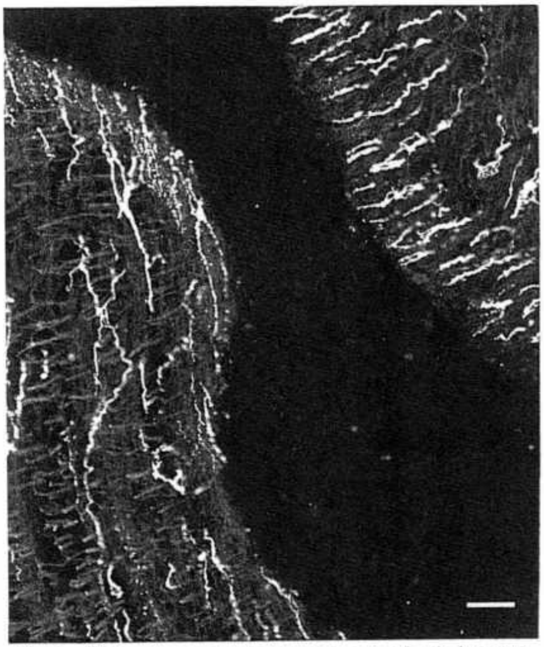


Fig 6 *Photomicrograph of a large proximal vein in a two month old child showing an extensive network of fascicles and nerve fibres that were immunoreactive for neuropeptide tyrosine throughout the vessel wall. Scale bar = 50 μm.*

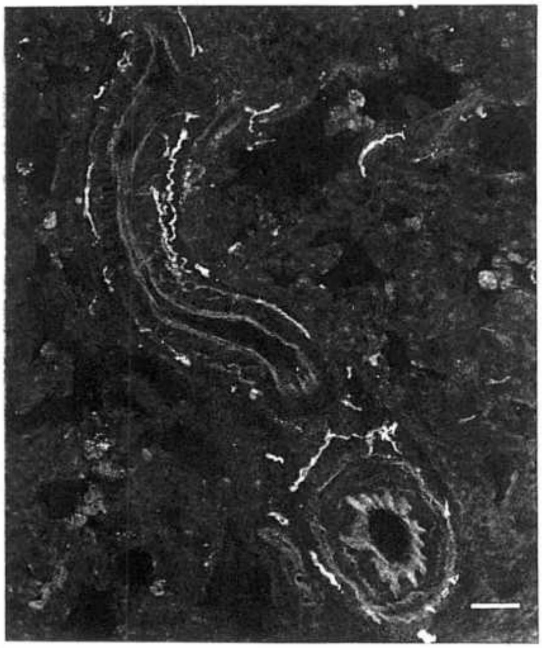


Fig 7 *Photomicrograph showing nerves that were immunoreactive for protein gene product 9·5 localised to the adventitial-medial border of abnormality thick walled intra-acinar arteries in a two month old child with pulmonary hypertension. Scale bar = 50 μm.*

hydroxylase and neuropeptide tyrosine immunoreactivity. Neuropeptide tyrosine has a direct effect mediating vasoconstriction and an indirect effect modulating noradrenergic vasoconstriction via both pre and post synaptic mechanisms.[21 22] In the muscular pulmonary arteries of the rabbit, neuropeptide tyrosine was found to potentiate noradrenaline evoked vasoconstriction,[23] but little is known about the distribution and density of specific neuropeptide tyrosine receptors in the pulmonary vasculature.

In children with pulmonary hypertension who were less than one year old, the arteries of the respiratory unit seemed to be prematurely innervated by sympathetic-like nerve fibres. Associated changes in the smooth muscle cells of these peripheral arteries also occur over a similar period of time. Cells which would normally be pericytes, intermediate cells, or smooth muscle cells with a synthetic phenotype become hypertrophied and have an increased concentration of myofilaments and dense bodies and thus show ultrastructural features typical of differentiated smooth muscle cells with a contractile phenotype.[3] Many of these changes are an acceleration of the normal pattern of development. In both the normal and pulmonary hypertensive lung, the development of the sympathetic innervation seems to occur in parallel with an increase in the amount of smooth muscle in peripheral arteries and with an increase in the differentiation of that muscle. Sympathetic nerves may be exerting a long term trophic effect on the vascular muscle cells. Certainly in culture, vascular smooth muscle cells undergo an accelerated maturation in the presence of sympathetic nerves and also show increased incorporation of protein in the presence of contractile agonists.[5 24]

In all the controls and children with pulmonary hypertension vasoactive intestinal peptide and somatostatin (presumed parasympathetic) and tachykinin and calcitonin gene related peptide (sensory) immunoreactive nerve fibres were more sparsely distributed than the relatively dense, presumed sympathetic innervation of the pulmonary vasculature. Previous studies showed both nerves and specific binding sites in the small muscular pulmonary arteries of the adult lung that were immunoreactive to vasoactive intestinal peptide.[25 26] In the present study, at all ages vasoactive intestinal peptide fibres seemed most abundant in the small muscular arteries just proximal to the respiratory unit—arteries that can be considered as the resistance vessels of the lung. Extensive innervation of these vessels suggests that the flow of blood into the respiratory unit and

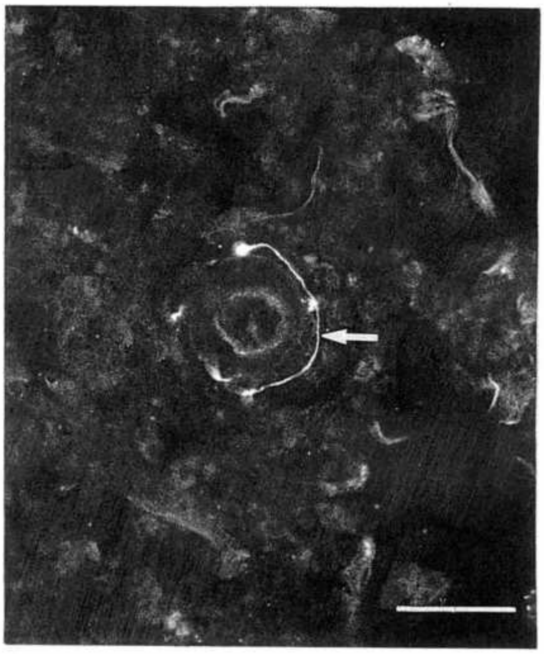


Fig 8 *Photomicrograph showing fibres (arrow) that were immunoreactive to neuropeptide tyrosine running around the adventitial border of an alveolar duct artery in a two month old patient with pulmonary hypertension. Scale bar = 50 μm.*

capillary bed is partly under neurogenic control.

Vasoactive intestinal peptide,[25 27] substance P,[28] and calcitonin gene related peptide[29] are all potent vasodilators and all have been shown to relax pulmonary arteries in man or other species. As with vasoactive intestinal peptide, specific binding sites for substance P[30] and calcitonin gene related peptide[31] have been localised to medial smooth muscle cells of human intrapulmonary arteries by in vitro autoradiography. Whether or not the action of the vasoactive peptides is endothelium-dependent is particularly important in the context of pulmonary hypertension because endothelial damage and denudation can be seen in the small muscular arteries of many pulmonary hypertensive children after the age of six months.[3] Substance P seems to require an intact endothelium[28 32] to be effective whereas vasoactive intestinal peptide and calcitonin gene-related peptide seem to be less endothelium dependent.[27 29] If in the children with pulmonary hypertension endothelial damage reduces the effectiveness of endothelial dependent vasodilator neuropeptides, this might explain why pulmonary hypertensive crises develop in some children but not others. All the patients with pulmonary hypertension had abnormally thick walled, prematurely innervated respiratory unit arteries. Numerous other vasoactive substances acting on and produced by the endothelium may be just as important. Studies on receptor localisation, density, and kinetics and on the interaction between vasoactive peptides, endothelium, and vascular smooth muscle in the immature lung are indicated.

The present study indicates that the vasoconstrictor peptide, neuropeptide tyrosine, is the predominant neuropeptide in the pulmonary circulation at all ages, in both the normal and pulmonary hypertensive lung. In infants with pulmonary hypertension, the premature innervation of peripheral, abnormally thick walled, pulmonary arteries may be important in the aetiology of pulmonary hypertensive crises—the vasoconstrictor episodes which characterise the postoperative course of many young children after intracardiac repair.

This work was supported by grants from the British Heart Foundation and the National Fund for Research into Crippling Diseases. SGH is supported by the British Heart Foundation.

References

1 Allen K, Haworth SG. Human postnatal pulmonary arterial remodelling: ultrastructural studies of smooth muscle cell and connective tissue maturation. *Lab Invest* 1988;**58**:702–9.

2 Allen K, Haworth S. Cytoskeletal features of immature pulmonary vascular smooth muscle cells and the influence of pulmonary hypertension on normal human development. *J Pathol* 1989;**158**:311–7.

3 Haworth S, Hall S, Burford B, Allen K, Mills A. The effect of pulmonary hypertensive congenital heart disease on the post-natal remodelling of the pulmonary vasculature [Abstract]. *J Am Coll Cardiol* 1988;**11** (suppl A):135A.

4 Wharton J, Haworth SG, Polak J. Postnatal development of the innervation and paraganglia in the porcine pulmonary arterial bed. *J Pathol* 1988;**154**:19–27.

5 Chamley J, Campbell GR, Burnstock G. Dedifferentiation, redifferentiation and bundle formation of smooth muscle cells in tissue culture: influence of cell number and nerve fibres. *J Embryol Exp Morphol* 1974;**32**:297–323.

6 Amenta F, Cavallotti C, Ferrante F, Tonelli F. Cholinergic innervation of the human pulmonary circulation. *Acta Anat (Basel)* 1983;**117**:58–64.

7 Kay K. Pulmonary vasculature and nerves. Comparative morphological features of the pulmonary vasculature in mammals. *Am Rev Respir Dis* 1983;**128**:S53–7.

8 Dey R, Shannon W, Said S. Localisation of VIP-immunoreactive nerves in airways and pulmonary vessels of dogs, cats and human subjects. *Cell Tissue Res* 1981;**220**:231–8.

9 Hua X-Y, Theodorsson-Northeim E, Brodin E, Lundberg J, Hokfelt T. Multiple tachykinins (neurokinin A, neuropeptide K and substance P) in capsaicin-sensitive sensory neurones in the guinea pig and rat. *Regul Pept* 1985;**13**:1–19.

10 Wharton J, Gulbenkian S, Mulderry P, *et al* Capsaicin induces a depletion of calcitonin gene-related peptide (CGRP)—immunoreactive nerves in the cardiovascular system of the guinea pig and rat. *J Auton Nerv Syst* 1986;**16**:289–309.

11 Sheppard MN, Polak JM, Allen JM, Bloom SR. Neuropeptide tyrosine (NPY): a newly discovered peptide is present in the mammalian respiratory tract. *Thorax* 1984;**39**:326–30.

12 Lundberg J, Martling C-R, Hökfelt T. Airways, oral cavity and salivary glands: classical transmitters and peptides in sensory and autonomic motor neurones. In: Bjorkland A, Höfelt T, Owman C, eds. *Handbook of chemical neuroanatomy,* vol 6. Amsterdam: Elsevier, 1988:391–444.

13 Wharton J, Gulbenkian S, Merighi A, *et al.* Immunohistochemical and ultrastructural localization of peptide-containing nerves and myocardial cells in the human atrial appendage. *Cell Tissue Res* 1988;**254**:155–66.

14 Gulbenkian S, Wharton J, Polak J. The visualisation of cardiovascular innervation in the guinea pig using an antiserum to protein gene product 9·5 (PGP 9 5). *J Auton Nerv Syst* 1987;**18**:235–47.

15 Wiedenmann B, Franke W. Identification and localization of synaptophysin, an integral membrane glycoprotein of Mr 38,000 characteristic of presynaptic vesicles. *Cell* 1985;**41**:1017–28.

16 Gulbenkian S, Wharton J, Hacker G, Varndell I, Bloom S, Polak J. Co-localisation of neuropeptide tyrosine

(NPY) and its C-terminal flanking peptide (CPON). *Peptides* 1985;**6**:1237–43.

17 Haworth SG, Hislop AA. Pulmonary vascular development: normal values of peripheral vascular structure. *Am J Cardiol* 1983;**52**:578–83.

18 Haworth SG, Hall SM, Chew M, Allen K. Thinning of fetal pulmonary arterial wall and postnatal remodelling: ultrastructural studies on the respiratory unit arteries. *Virchows Arch [A]* 1987;**411**:161–71.

19 Burnstock G. Neuropeptides as trophic factors. In: Polak JM, Lindenlaub, E, eds. *Systemic role of regulatory peptides*. Stuttgart: FK Schattauer Verlag, 1982:423–40.

20 Keatinge W, Torrie C. Action of sympathetic nerves on inner and outer muscle of sheep carotid artery, and effect of pressure on nerve distribution. *J Physiol (Lond)* 1976;**257**:699–712.

21 Pernow J, Saria A, Lundberg J. Mechanisms underlying pre- and postjunctional effects of neuropeptide Y in sympathetic vascular control. *Acta Physiol Scand* 1986;**126**:239–49.

22 Ekblad E, Edvinsson L, Wahlestedt C, Uddman R, Hakanson R, Sundler F. Neuropeptide Y co-exists and co-operates with noradrenaline in perivascular nerve fibres. *Reg Pept* 1984;**8**:225–35.

23 Wahlestedt C, Edvinsson L, Ekblad E, Hakanson R. Neuropeptide Y potentiated noradrenaline-evoked vasoconstriction: mode of action. *J Pharmacol Exp Ther* 1985;**234**:735–41.

24 Geisterfer A, Peach M, Owens G. Angiotensin II induces hypertrophy, not hyperplasia, of cultured rat aortic smooth muscle cells. *Circ Res* 1988;**62**: 749–56.

25 Barnes PJ, Cadieux A, Carstairs JR, Greenberg B, Polak JM, Rhoden K. Vasoactive intestinal peptide in bovine pulmonary artery: localisation, function and receptor autoradiography. *Br J Pharmacol* 1986;**89**: 157–62.

26 Carstairs J, Barnes PJ. Visualisation of vasoactive intestinal peptide receptors in human and guinea pig lung. *J Pharmacol Exp Ther* 1986;**239**:249–55.

27 Greenberg B, Rhoden K, Barnes P. Relaxant effects of vasoactive intestinal peptide and histidine isoleucine in human and bovine pulmonary arteries. *Blood Vessels* 1987;**24**:45–50.

28 Tanaka D, Grunstein M. Vasoactive effects of substance P on isolated rabbit pulmonary artery. *J Appl Physiol* 1985;**58**:1291–7.

29 McCormack D, Mak J, Barnes P. Calcitonin gene-related peptide (CGRP) causes non-endothelial dependent relaxation of human pulmonary arteries and veins [Abstract]. *Am Rev Respir Dis* 1988; **137**:372.

30 Carstairs J, Barnes P. Autoradiographic mapping of substance P receptors in lung. *Eur J Pharmacol* 1986;**127**:295–6.

31 Mak J, Barnes P. Autoradiographic localization of calcitonin gene-related peptide (CGRP) binding sites in human and guinea pig lung. *Peptides* 1988;**9**: 957–63.

32 D'Orleans-Juste P, Dion S, Drapeau G, Regoli D. Different receptors are involved in the endothelium-mediated relaxation and smooth muscle contraction of the rabbit pulmonary artery in response to substance P and related neurokinins. *Eur J Pharmacol* 1985;**125**:37–44.

Br Heart J 1989;62:361–6

Transvenous ablation of atrioventricular conduction with a low energy power source

EDWARD ROWLAND, DAVID CUNNINGHAM, ARIF AHSAN, ANTHONY RICKARDS

From the National Heart and Lung Institute and National Heart and Chest Hospitals, London

SUMMARY A power source modified to increase voltage delivery and minimise arcing (for a given energy) was used for transvenous ablation of atrioventricular conduction to control refractory supraventricular arrhythmias in 14 patients. Twelve had atrial fibrillation or flutter, one had atrioventricular nodal reentry tachycardia, and the other had permanent junctional reentry tachycardia. Despite treatment with 5–7 (median 6) antiarrhythmic drugs symptoms had persisted in all the patients. Cathodal discharges of 0·5–39·5 J were delivered to the distal electrode (in one case in parallel with the middle electrode). In all patients shocks produced complete atrioventricular block; this was permanent in eleven (79%). Four patients required a second procedure. In one patient, only a transient atrioventricular block could be produced and catheter ablation with a conventional power source also failed. In the other two atrioventricular conduction was modified such that previously ineffective treatment produced satisfactory control of heart rate. The cumulative energy delivered to those in whom permanent complete heart block resulted ranged from 3·6 to 97·8 (mean 38·3) J with a mean of three shocks (range 1–7) delivered per patient. During follow up of 1–28 (mean 14) months 11 patients remained in complete heart block and free of arrhythmia.

Transvenous ablation of atrioventricular conduction conventionally uses high energy discharges generated by a standard defibrillator and has become an accepted and effective method of creating complete atrioventricular block in patients with refractory supraventricular arrhythmias.[1–4] The precise mechanism by which these high energies destroy the atrioventricular conduction system is unknown but high energy discharges produce an explosive flash (arcing) that is associated with a raised local temperature and a high intensity pressure wave.[5 6] Examination of the Ablation Registry showed that this technique achieved complete heart block in 63% of patients and that the mean cumulative stored energy required was 611 J.[4] The recommended conventional technique uses one or more shocks of 150–300 J delivered between one electrode of a standard 6F or 7F pacing catheter and a back plate.[7] Several adverse effects have been reported including myocardial rupture,[8] and there is concern about intravascular haemolysis[9] and right ventricular dysfunction,[10] and that gas bubbles may be produced in both ventricles immediately after the shock.[11] Although it is not clear which properties of the high energy cause the desired clinical effect it seems likely that many of these adverse effects result from the pressure wave.

We have designed a power source that shortens the energy delivery time in order to produce shocks that increase peak voltage and current for a given energy.[12] Our previous work has shown that this energy source has a higher arcing threshold than a standard defibrillator, with the result that local electrical effects predominate over those resulting from arcing (barotrauma).[13]

Patients and methods

Fourteen patients with drug refractory supraventricular arrhythmias underwent attempted transvenous ablation of atrioventricular conduction. Twelve had paroxysmal or established atrial fibrillation or flutter, one had paroxysmal atrioventricular nodal

Requests for reprints to Dr Edward Rowland, National Heart Hospital, Westmoreland Street, London W1M 8BA.

Accepted for publication 2 May 1989

Table *Data on patients who had ablation of the atrioventricular pathway by the new ablater*

Case	*Age*	*Sex*	*Diagnosis*	*Previous treatment*	*Test shocks (J)*	*Definitive shocks (J)*	*Clinical outcome*	*Follow up (mnth)*
1	54	M	PJRT	DVQFBADs	2 2	37·5	1	28
2	69	F	PAFl	DVBASDsQ	2 0	5·1	2	27
3	63	M	PAFl	DVAQP	0 5	3 1	1	24
4	61	M	PAF	DVBASQ	1 4	5 7/21 8/29 3/16·5/16 5/27 0/27 1/29 4/38 9	3	1*
5	52	F	PAF	DVBASDsF	(1) 1·6 (2) —	(1) 6 5 (2) 22	3 1	18
6	75	M	AF	DVASDsFP	—	6 9/17 4/38 2	2	17
7	65	M	PAF	QDBVSA	1 6	19·9	1	14
8	69	M	PAF	DVBDsA	1 6/1 6	26 3/27 7	1	14
9	63	F	EAT	DVDsAP	1 4	21 1	1	14
10	50	F	AF	DVADsF	(1) 1·5/1 6 (2) 1 6	(1) 22 3/34·0 (2) 36 8	3 1	12
11	66	F	PAF	DVBADsQ	(1) — (2) —	(1) 22 8/21 4 (2) 34 0	3 1	10
12	72	F	PAF	DVBADsF	(1) 1·0/1 3/2·0 (2) —	(1) 4 4 (2) 12 0/20 1/20	3 1	9
13	69	M	PAFl	DVBAF	1 2	8·9	1	7
14	65	F	AVNRT	DVBDsQAP	1 3/2 4	—	1	7

Diagnosis PJRT, permanent junctional reentry tachycardia, PAFl, paroxysmal atrial flutter, PAF, paroxysmal atrial fibrillation, EAT, ectopic atrial tachycardia; AF, established atrial fibrillation, AVNRT, atrioventricular nodal reentry tachycardia
Drugs. D, digoxin, V, verapamil, Q, quinidine, B, β blockers, Ds, disopyramide; F, flecainide, S, sotalol, P, propafenone, A, amiodarone
All energies are the delivered values Where second procedures were performed the values are indicated for the first (1) and second (2) procedures.
Clinical outcome 1, complete heart block; 2, impaired atrioventricular conduction, 3, no effect
*Surgical ablation of atrioventricular conduction

reentry tachycardia, and one had the permanent form of junctional reentry tachycardia. All patients had received at least five antiarrhythmic drugs, including amiodarone, which had either been ineffective or had been stopped because of side effects (table). None had undergone previous transvenous ablation. Antiarrhythmic drugs were stopped before the procedure in 11 patients—the other three were continued on atrial stabilising drugs to prevent atrial arrhythmias during ablation.

PROCEDURE

After informed consent had been obtained and premedication given a small (4F or 5F) pacing electrode was introduced percutaneously via the right subclavian vein, positioned at the apex of the right ventricle, and used for temporary ventricular pacing. The His bundle electrogram was recorded with a 7F USCI tripolar electrode in 13 cases (a 6F tripolar electrode was used in the other) and positioned adjacent to the tricuspid valve. Three patients were in atrial fibrillation at the time of the procedure and an adequate (⩾200 μV). His bundle could not be identified; external DC cardioversion was performed in order to restore sinus rhythm. In these a third electrode was used for temporary atrial pacing to maintain atrial stability after DC cardioversion.

Bipolar and unipolar electrograms from the tripolar electrode catheter were recorded and the position of the electrode catheter adjusted until the largest His bundle electrogram was recorded on the distal pair. Unipolar electrograms were also recorded to ensure that the distal electrode had the largest His bundle component. If the atrial electrogram on the bipolar signal was lower in amplitude than the His bundle potential the catheter was withdrawn towards the atrium.

When the optimal His bundle electrode catheter position had been identified the patient was anaesthetised, a defibrillator plate placed under the left scapula, and the His bundle electrogram re-checked. A blood sample was then taken for estimation of the serum concentration of creatine kinase (total and MB fraction).

The power source used in this study was a specially designed ablater (Cardiac Recorders CR60), the characteristics of which have been described.[12] This device produces a capacitive discharge without inductance modification. We used resistive attenuators and precision differential amplifiers to measure the delivered voltage and current: the waveforms were recorded on a Gould 1425 digital storage oscilloscope and data (8 bit) transferred on a serial link to a microcomputer (Hewlett-Packard 150) for computation of energy, power, and impedance. All shocks were delivered synchronously with the R wave of a surface electrocardiogram lead.

The cathodal output of the ablater was connected to the distal electrode of the His bundle electrode catheter and "test" shocks of 0·5, 1, or 2 J were selected and delivered to test the responsiveness of atrioventricular conduction. If right bundle branch block was produced the His bundle electrode catheter was withdrawn towards the atrium. In one case the electrode catheter prolapsed into the atrium when it was withdrawn; the electrode catheter was therefore positioned optimally and further shocks were delivered through the distal and middle electrodes which were connected in common. The response of the atrioventricular conduction system was observed for up to 25 minutes.

When complete heart block did not persist "definitive" shocks of 5, 10, 20, 30, or 40 J were then selected and delivered, the energy level chosen depending on the degree and duration of heart block produced by the test shock. Shocks were delivered in the same configuration as that used for the test shocks. The effect of the definitive shock was monitored for 25 minutes and if complete heart block persisted no further shocks were delivered. If atrioventricular conduction returned further shocks of 20, 30, or 40 J were administered.

The patients were observed for 24 hours and a permanent rate responsive ventricular demand pacemaker (VVI) or atrioventricular sequential pacemaker was implanted when third degree atrioventricular block persisted or when evidence of considerable impairment of atrioventricular conduction remained. In those in whom atrioventricular conduction returned to normal the ablation procedure was repeated. On this occasion test shocks were not used; an energy level above that used at the first ablation attempt was selected (that is, 20, 30, or 40 J).

After each ablation procedure blood was collected for estimation of creatine kinase at eight and 24 hours.

Results

Permanent complete heart block was achieved in 11 patients, there was no change in atrioventricular conduction in one patient, and in the other two patients atrioventricular conduction was modified. Fifty shocks were delivered in the 14 patients and the mean cumulative energy delivered was 50·4 (range 3·6–212·2) J. Figure 1 shows the overall persistence of atrioventricular conduction in response to the shocks. In those in whom permanent complete heart block was achieved the mean cumulative energy delivered was 38·3 (range 3·6–97·7) J and the mean number of shocks required was three (range 1–7).

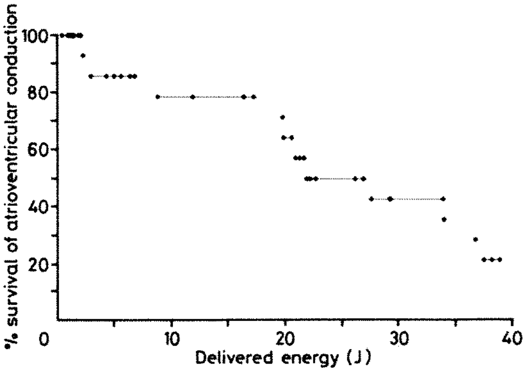


Fig 1 *Survival of atrioventricular conduction in response to increasing energy. Each of the fifty shocks used is plotted. In three patients (21%) atrioventricular conduction survived intact. For the purposes of the survival curve the highest energy shock delivered to a patient who attained permanent heart block was assumed to have been successful.*

TEST SHOCKS

Test shocks were not used in two patients because the electrode catheter was believed to be in an unstable position and creation of a heart block was thought to be more pressing. In one patient the test shock (delivered energy 2·4 J) produced permanent complete heart block, associated after 18 hours with a narrow QRS escape rhythm of 55 beats/min. In two patients the test shock resulted in transient right bundle branch block and withdrawal of the His bundle electrode toward the atrium was associated with transient complete heart block when a subsequent test shock was used. Therefore in 11 patients delivered energies of 0·5–2·2 J produced transient interruption of atrioventricular conduction which lasted for 30 seconds to 23 minutes.

DEFINITIVE SHOCKS

Between one and nine shocks ranging from 3·1 to 38·9 J were delivered in 13 patients. In six permanent complete heart block was achieved with a single definitive shock (delivered energy 3·1–37·5 J) (fig 2). In one patient only transient interruption of atrioventricular conduction could be achieved. In this patient the His bundle electrogram remained small (100 μV), despite repositioning of the electrode catheter, and repeated shocks of increasing intensity in various positions did not interrupt atrioventricular conduction. Electrode catheter ablation performed subsequently with a conventional power source (300 J shocks) was equally ineffective. In the remaining six patients transient atrioventricular block resulted from the first definitive shock and one or two further shocks were required to produce complete heart block for the duration of the observation period.

Four patients had a second ablation procedure performed because complete heart block did not

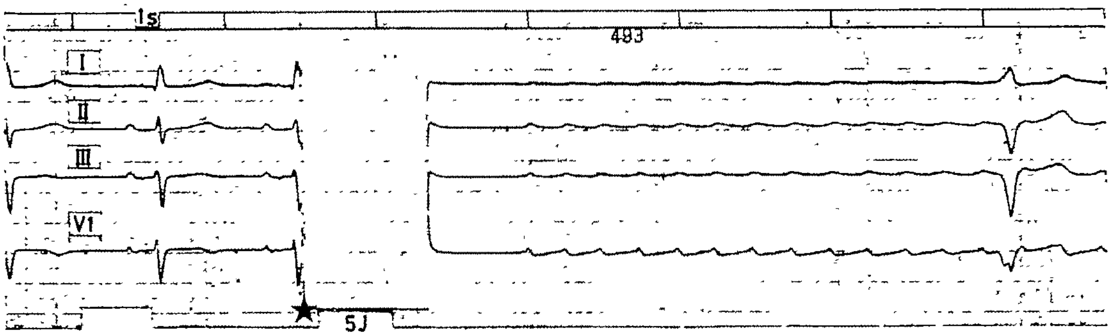


Fig 2 *In patient 2 (a woman of 69) a synchronised shock of 5 J(*) was delivered during sinus rhythm and resulted in complete heart block, with simultaneous induction of atrial flutter. Electrocardiographic leads I, II, III, and VI are shown.*

persist after the first attempt and atrioventricular conduction returning within 2–6 hours. Complete heart block was achieved in all of them at the second procedure.

In three patients atrial fibrillation was induced by one of the ablation shocks but non-sustained or sustained ventricular tachycardia or ventricular fibrillation was not induced in any of them.

In 11 patients serum concentrations of creatine kinase were measured before and after the procedure and in two there was a significant rise, but both patients had had multiple transthoracic cardioversions to establish sinus rhythm during the ablation procedure. In none of the patients was there a significant increase in the creatine kinase MB fraction.

FOLLOW UP

Complete heart block was maintained in 11 patients during follow up of 7–28 (mean 14) months. In each patient either a rate responsive ventricular demand (10 patients) or atrioventricular sequential pacemaker was implanted. None of these patients is being treated with antiarrhythmic agents and none has symptomatic palpitation. One patient had an uncomplicated anterior myocardial infarction 11 months after the ablation and another experienced an episode of persistent chest pain five months later but had no enzyme evidence of infarction. Surgical ablation of the His bundle was successful in the patient in whom both modified and conventional ablation failed.

In two patients atrioventricular conduction seemed to return late after the ablation but when it did there was evidence of impaired conduction. In patient 6 atrial fibrillation recurred 24 hours after the procedure and was conducted at a mean ventricular rate of 68 beats/minute compared with 122 beats/minute before ablation. Although the resting and exercise heart rates during atrial fibrillation subsequently increased they remained well controlled on digoxin. Before ablation they had remained uncontrolled despite combined treatment with digoxin and verapamil. This patient was not paced and repeated ambulatory electrocardiographic recordings did not show prolonged pauses. The other patient who presented with paroxysmal atrial flutter, was in complete heart block after a 5·1 J discharge and this was thought to be present at the end of the observation period. Closer analysis showed that there was high degree (6:1) atrioventricular block at the end of the procedure; subsequently paroxysms of atrial flutter were conducted slowly. A symptomatic episode of palpitation recurred, however, six months after the ablation and atrial flutter with 2:1 atrioventricular block was documented. Treatment with digoxin was started and further attacks of atrial flutter were associated with high degree atrioventricular block.

Discussion

Electrode catheter ablation of atrioventricular conduction is used to treat patients with supraventricular arrhythmias who continue to have symptoms while taking medical treatment or who are intolerant of medical treatment. Data collected by the Ablation Registry showed that permanent complete heart block was produced in 63% of 360 patients who had ablation of the atrioventricular tract (mean 611 J/patient).[4] Similar results were reported from the United Kingdom and France.[3 14] Complications may, however, follow the use of these high energy shocks. Ventricular arrhythmias may occur in the short term as may hypotension and cardiac perforation.[4-8] There is a short lived rise in cardiac enzymes[1-4] and evidence that right ventricular function may be impaired in the long term.[10] Follow up of the registry patients also showed that 2% died suddenly in the mean follow up period of nine months.[4]

A defibrillator is conventionally used as the power source for catheter ablation, despite the fact that to minimise injury to the chest wall it has a waveform that is designed to limit the peak current for a given energy. Because the intention of catheter ablation is to cause localised damage this waveform may not be appropriate.

Several physical events result from the discharge of a high voltage through a small intracardiac electrode.[5,6] The precise physical features of the energy that cause damage are unknown. After discharge of the defibrillator an intense electric field surrounds the intracardiac electrode and current flow results in resistive heating. With all but the lowest defibrillator energies arcing will occur across the gas that builds up around the electrode as a consequence of this local heating. Arcing will result in a high pressure shock wave that will propagate without local attenuation.[15] The series inductance in the output circuit of a standard defibrillator retards the rate of discharge of the capacitor and increases the time to peak voltage. This allows a high voltage to be present when insulating gas has formed around the electrode and therefore arc formation is encouraged. The modified ablater was designed to deliver similar voltage but over a shorter interval, in part to allow delivery of the maximum amount of energy before the build up of gas. This design permits higher voltage and current to be delivered for a given energy and allows the local effects of cellular electric field dielectric breakdown,[16] ionisation, and heating to predominate over barotrauma.[12] It is likely that the rise in temperature is limited to such an extent that it does not produce any important tissue damage.

Our results indicate that electrode catheter ablation of atrioventricular conduction is successful in a high percentage of patients at considerably lower energies than previously reported. We measured the delivered voltage and current and were therefore able to compute delivered energy. Such measurements have not been systematically reported before and therefore comparisons with other series cannot easily be made. In most previous studies only the stored energies or the energy delivered to a nominal resistance were recorded. It is difficult, therefore, to establish the relation between the voltages and currents associated with the energies used in this study and those seen with conventional defibrillator shocks. Trantham *et al*, however, did record voltage and current in 12 patients undergoing electrode catheter ablation by conventional shocks of 200 and 300 J—the mean peak voltages were 2·16 and 2·40 kV and the mean peak currents were 42·2 and 58·2 A respectively.[17] In those patients in our series in whom a single definitive shock caused permanent complete heart block, the mean energy was 16·4 (range 2·4–37·5) J, the mean peak voltage 1·85 (range 0·79–2·78) kV, and the mean peak current 15·5 (range 4·6–25) A.

We used standard electrodes and techniques for His bundle recording as well as standard criteria for determining the optimal site for energy delivery. Other studies have also attempted to reduce the energy requirements for electrode catheter ablation of atrioventricular conduction. Holt *et al* used the specially shaped design of helical permanent pacing electrodes to ensure both a closer contact with the target and direct the energy.[18] Four shocks of 50 J each in 10 patients achieved complete heart block in seven. Polgar *et al* used a suction electrode to obtain close contact with the His bundle and achieved complete heart block in three of five patients with single shocks of 50–150 J.[19] Although the serum concentration of creatine kinase was raised the concentration was lower than in a comparative group undergoing atrioventricular ablation in the conventional method. McComb *et al* attempted electrode catheter ablation of atrioventricular conduction in seven patients at low levels of energy (20–50 J) from a defibrillator in an attempt to impair but not destroy atrioventricular conduction.[20] Single initial shocks of 50 J, however, produced permanent complete heart block in three patients.

The absence of a rise in cardiac enzymes in our patients is intriguing. The *peak* voltages (and associated peak currents) seen in our patients are equivalent to energies 5–10 times higher when a standard defibrillator is used. Therefore the electric field intensities are similar to those encountered when the conventional technique is used and cardiac enzymes are increased.[17] If as seems possible myocardial damage is produced as a consequence of the diffuse effect of a shock wave, possibly by means of cavitation, this provides further circumstantial evidence that this modified waveform reduces the arcing tendency and results in a lower pressure shock wave for a given peak voltage.

Our protocol for determining the efficacy of individual shocks differed from reports of other methods. We used test shocks in an attempt to determine whether the catheter was positioned at the correct level of the conduction system and additionally to provide a guide to the responsiveness of atrioventricular conduction to electrical discharge. It is clear that the energy-response relation with our technique is wide and presumably influenced by the proximity of the electrode to the conducting system. Whether the amplitude of the His bundle electrogram is a useful guide to proximity remains controversial. In some studies it correlated with clinical efficacy[2] while in others no relation was found.[3] Clearly no individual value for the amplitude of the His bundle potential will determine successful catheter ablation. We attempted on each occasion to position the electrode catheter so that it recorded an amplitude $>200\ \mu V$, and in two of the three patients in whom complete heart block was not achieved the His bundle potential was $<200 \mu V$.

Test shocks may dislodge the electrode. If this happens the catheter will have to be repositioned while the His bundle is temporarily disrupted and therefore not producing as large an electrical signal. In fact movement of the electrode catheter was slight at these low energies, but during the shocks and for the observation period afterwards the operator held the catheter to maintain its position. If dislodgement had been an important problem we would have expected a higher incidence of repeat procedures. But only four (29%) of 14 required second ablations compared with 37% and 58% in larger series.[3,4]

This study showed that permanent ablation of atrioventricular conduction can be achieved with a purpose built ablater. This power source achieved complete heart block with cumulative energies that were several times lower than those required with a conventional defibrillator. This power source, which was designed to optimise the local electrical effects and reduce the tendency to arcing, gave results that suggested that arcing is not essential for the ablation of atrioventricular conduction. We do not know whether avoidance of arcing and its attendant effects will improve the long term outcome of patients undergoing ablation.

References

1 Scheinman MM, Morady F, Hess S, Gonzalez R. Catheter-induced ablation of the atrioventricular junction to control refractory supraventricular arrhythmias. *JAMA* 1982;**248**:851–5.

2 Gallagher JJ, Svenson RH, Kasell JH, *et al.* Catheter technique for closed-chest ablation of the atrioventricular conduction system: a therapeutic alternative for the treatment of refractory SVT. *N Engl J Med* 1982;**306**:194–200.

3 Nathan AW, Bennett DH, Ward DE, Camm AJ. Catheter ablation of atrioventricular conduction. *Lancet* 1984;**i**:1280–4.

4 Evans GT, Scheinman MM. Catheter ablation of ventricular tachycardia foci: a report of the percutaneous cardiac mapping and ablation registry [Abstract]. *Circulation* 1986;**74**(suppl II):460.

5 Boyd EGCA, Holt PM. An investigation into the electrical ablation technique and a method of electrode assessment. *PACE* 1985;**8**:815–23.

6 Bardy GH, Coltorti F, Ivey TD, *et al.* Some factors affecting bubble formation with catheter-mediated defibrillator impulses. *Circulation* 1986;**73**:525–38.

7 Scheinman MM. Catheter ablation for patients with cardiac arrhythmias. *PACE* 1986;**9**:551–64.

8 Fisher JD, Kim SG, Matos JA, *et al.* Complications of catheter ablation of tachyarrhythmias: occurrence, protection and prevention. *Clin Prog Electrophysiol Pacing* 1985;**3**:292–8.

9 Holt PM, Boyd EGCA. Hematologic effects of the high-energy endocardial ablation technique. *Circulation* 1986;**73**:1029–36.

10 Schofield PM, Bowes RJ, Brooks N, Bennett DH. Exercise capacity and spontaneous heart rhythm after transvenous fulguration of atrioventricular conduction. *Br Heart J* 1986;**56**:358–65.

11 Rowland E, Foale R, Nihoyannopoulos P, Perelman M, Krikler DM. Intracardiac contrast echoes during transvenous His bundle albation. *Br Heart J* 1985;**53**:240–2.

12 Cunningham D, Rowland E, Rickards AF. A new low energy power source for catheter ablation. *PACE* 1986;**9**:1384–90.

13 Ahsan AJ, Cunningham D, Rowland E, Rickards AF. Catheter ablation without fulguration: design and performance of a new system. *PACE* 1989;**12**(Part II):131–5.

14 Lévy S, Bru P. Interruption électrique par voie percutanée de la conduction auriculo-ventriculaire normale. Analyse des cas français. *Arch Mal Coeur* 1986;**79**:1145–50.

15 Cunningham D, Rowland E, Rickards AF. Lack of shock wave absorption after high energy catheter discharge suggests that barotrauma is a myth [Abstract]. *Circulation* 1987;**76**(suppl IV):407.

16 Jones JL, Proskauer CC, Paull WK, Lepeschkin E, Jones RE. Ultrastructural injury to chick myocardial cells in-vitro following "electrical countershock". *Circ Res* 1980;**46**:387–49.

17 Trantham JL, Gallagher JJ, German LD, Broughton A, Guarneri T, Kasell J. Effects of energy delivery via a His bundle catheter during closed chest ablation of the atrioventricular conduction system. *J Clin Invest* 1983;**72**:1563–74.

18 Holt PM, Boyd EGCA, Crick J, Sowton E. Low energies and Helifix electrodes in the successful ablation of atrioventricular conduction. *PACE* 1985;**8**:639–45.

19 Polgar P, Worum F, Kovacs P, Lorincz I, Bekassy Sz, Peterffy A. A new technique for closed-chest human His bundle ablation using suction electrode catheter and DC shock. In: Perez-Gomez F, ed. *Cardiac pacing, electrophysiology, tachyarrhythmias*. New York: Futura Media Services, 1985:1582–7.

20 McComb JM, McGovern BA, Garan H, Ruskin JN. Modification of atrioventricular conduction using low energy transcatheter shocks [Abstract]. *J Am Coll Cardiol* 1985;**5**:454.

Br Heart J 1989;**62**:367–71

Clinical efficacy of intravenous amiodarone in the short term treatment of recurrent sustained ventricular tachycardia and ventricular fibrillation

WILHELM SCHÜTZENBERGER, FRANZ LEISCH, KLAUS KERSCHNER,
WOLFGANG HARRINGER, WALTER HERBINGER

From the 1 Medizinische Abteilung des Allgemeinen Krankenhauses der Stadt Linz, Austria

SUMMARY The clinical efficacy of intravenous amiodarone in terminating sustained ventricular tachycardia and in preventing recurrences of ventricular tachycardia and ventricular fibrillation was evaluated in 26 patients. All of them presented with organic heart disease accompanied by depressed left ventricular function. Intravenous amiodarone terminated spontaneous ventricular tachycardia in eight of 19 patients. Fifteen of the 26 patients had had at least one episode of ventricular tachycardia or ventricular fibrillation each day in the period immediately before the intravenous administration of amiodarone. Amiodarone controlled ventricular tachycardia or ventricular fibrillation in nine of these 15 patients; in three further cases it was successful when supplemented by additional administration of a previously ineffective antiarrhythmic drug and ventricular pacing. Two patients died despite these measures. In one, the amiodarone infusion had to be stopped because of an arrhythmogenic effect. Sustained deterioration of haemodynamic function or of pre-existing intraventricular conduction disturbances was never seen.

Intravenous amiodarone was effective in terminating sustained ventricular tachycardia and in preventing frequent episodes of ventricular arrhythmia that were refractory to other antiarrhythmic drugs.

Long term treatment with oral amiodarone is effective in ventricular tachycardia and ventricular fibrillation refractory to conventional antiarrhythmic drugs.[1-3] Prolonged administration is required to achieve these antiarrhythmic effects, and oral amiodarone is not an appropriate treatment for acute tachycardia.[4] Intravenous amiodarone, however, had a rapid effect on supraventricular tachycardias.[5 6] Its role in the short term treatment of life threatening ventricular arrhythmias has not yet been determined. We report the results of using intravenous amiodarone for the termination and short term control of recurrent sustained ventricular tachycardia and ventricular fibrillation.

Patients and methods

We treated 26 patients (table 1) with recurrent sustained ventricular tachycardia or ventricular fibrillation with a standardised dose of intravenous amiodarone.

Table 2 lists the antiarrhythmic agents that failed to suppress tachycardia before intravenous amiodarone was tried. The following were administered: intravenous lignocaine (a loading dose of 1 to 2 mg/kg body weight followed by a continuous infusion of 2–4

Table 1 *Clinical features of 26 patients treated with intravenous amiodarone*

Variable	*Result*	
Males/females	19/7	
Age (yr) (mean (1 SD))	59	(10)
Heart disease:		
Coronary heart disease	21	
Previous myocardial infarction	19	
Ventricular aneurysm	7	
Dilated cardiomyopathy	3	
Hypertensive heart disease	1	
Valvar heart disease	1	
Ejection fraction (%) (mean (1 SD))	30·9	(12·9)
Previous DCC (n) (mean (1 SD))	6·4	(7·7)

DCC, direct current countershock.

Requests for reprints to Dr Wilhelm Schützenberger, Allgemeines Krankenhaus der Stadt Linz, Krankenhausstrasse 9, 4020 Linz, Austria.

Accepted for publication 25 April 1989

Table 2 *Unsuccessful drug treatment*

Case	*Intravenous*	*Oral*
1	L, P, M	F, A
2	L, P	—
3	L, P	M
4	—	P, M, F
5	L, M	P, A
6	L, M	P, Q
7	L, P	A
8	L, P, M	A, F
9	L, P, M	—
10	L, P	M
11	—	P, Q, M, F
12	L, P, M	A
13	—	P, A, M, F
14	L	M, P
15	L	—
16	—	P, M, A, F
17	L, P, M	A, F
18	L, P, M	—
19	L, P, M	—
20	L, P, M	—
21	L	P, D
22	L, P, M	—
23	L, P, M	—
24	L, P	—
25	L, P, M	—
26	L, P	D, F

A, prajmalium bitartrate; D, disopyramide; F, flecainide; L, lignocaine, M, mexiletine; P, propafenone; Q, quinidine.

mg/min); intravenous mexiletine (a loading dose of 100–250 mg, followed by 250 mg for the next hour, another 250 mg for the next two hours, and subsequently a continuous infusion of 1 to 2 mg/min); intravenous propafenone (a loading dose of 1 mg/kg body weight followed by a continuous infusion of 0·5–1 mg/min); oral prajmalium bitartrate (80 mg/day); oral disopyramide (400 mg/day); oral flecainide (200–300 mg/day); oral mexiletine (a loading dose of 1000 mg in the first 24 hours followed by 600 mg/day); oral propafenone (900 mg/day); oral quinidine 1·2 g/day. Amiodarone was given as follows: 5 mg/kg body weight in the form of a short term infusion within 20 minutes, followed by a continuous intravenous infusion of 1050 mg over 24 hours. Oral treatment was started on the second day with 600–800 mg/day for the next 13 days, followed by a maintenance dose of 400 mg/day. The electrocardiogram and blood pressure were monitored continuously in the coronary care unit. The last electrocardiogram recorded before the administration of intravenous amiodarone and the one immediately after the conclusion of the 24 hour amiodarone infusion were used for the electrocardiographic diagnosis.

Serum concentrations of amiodarone and desethyl amiodarone were measured by high pressure liquid chromatography.

The results were analysed for statistical significance by Student's t test.

Results

SHORT TERM CONVERSION OF SUSTAINED VENTRICULAR TACHYCARDIA TO SINUS RHYTHM

We attempted to terminate a ventricular tachycardia with intravenous amiodarone in 19 of our 26 patients. Termination of ventricular tachycardia was not seen in any of them without medical or electrical measures. All of these patients were haemodynamically stable at the beginning of the infusion. Electrical cardioversion was performed whenever the ventricular tachycardia was not terminated 60 minutes after the start of intravenous amiodarone or whenever the patient became haemodynamically unstable. The intravenous amiodarone was effective in terminating a spontaneous ventricular tachycardia in eight out of 19 patients within 31·1 (20) minutes. The termination was preceded by a decrease in the tachycardia cycle length in three patients, but occurred abruptly without prior reduction of cycle length in the remaining five. Comparison of the tachycardia rates shows that the mean value (161·9 (19·0)/min) was significantly lower in the group in which drug administration terminated the arrhythmia ($p < 0·05$) than in the patients who ultimately had to be treated with cardioversion (187·5 (24·7)/min). The difference in ejection fractions between both groups (drug treatment 25·8 (8·2)%, electrical cardioversion 31·7 (9·6)%) was not statistically significant.

PREVENTION OF FREQUENT RECURRENCES OF VENTRICULAR TACHYCARDIA AND VENTRICULAR FIBRILLATION

Fifteen of the 26 patients had at least one episode of ventricular tachycardia or ventricular fibrillation every day in the period (3–8 days) immediately preceding the intravenous amiodarone treatment. Because of severe heart failure, three out of the 15 were being treated with dopamine or dobutamine before the amiodarone infusion. In nine of the 15 patients tachycardia was suppressed solely with intravenous amiodarone. Six, however, continued to have episodes of sustained ventricular tachycardia or ventricular fibrillation during the first 24 hours without change in cycle length. These could not be suppressed even with a further short term infusion. In three of the six patients short term control of the arrhythmia was achieved by supplementing the treatment with a previously ineffective antiarrhythmic drug and ventricular pacing. Despite these measures two patients continued to have frequent episodes of the same arrhythmia they showed before treatment and they died of an arrhythmic cause. In the sixth patient, the amiodarone infusion had to be stopped because of an increase in ventricular tachycardia with transition to ventricular fibrillation. During the second and third week three patients had repeated recurrences of spontaneous clinical ventricular tachycardia on oral amiodarone treatment despite combination with other antiarrhythmic agents. Catheter electrode ablation was attempted in one. This proved unsuccessful, however, and an antitachycardia pacemaker had to be implanted. Coronary bypass surgery and an aneurysmectomy were performed in the other two and in the patient who showed an arrhythmogenic effect in response to amiodarone.

The following side effects were seen: thrombophlebitis on seven occasions, flush once, sinus arrest after electrical cardioversion once, and an increase of arrhythmia once. In the patient with the sinus arrest a normal sinus rhythm was restored immediately after the intravenous administration of 1 mg atropine. Hypotension, which we saw five times during short term infusion, and persistent ventricular tachycardia were rapidly eliminated by cardioversion.

ELECTROCARDIOGRAPHIC FINDINGS

Table 3 shows that the RR and PR intervals were not affected by intravenous amiodarone. Neither was the QTc time nor the QRS duration. Eleven of the 26 patients had conduction disorders before the intravenous administration of amiodarone: first degree atrioventricular block in three cases, right bundle branch block in two, and a left bundle branch block in two. Two further patients had an incomplete right bundle branch block, and two an incomplete left bundle branch block. Intravenous amiodarone, however, never caused a deterioration in atrioventricular or intraventricular conduction in any of the 11 patients with pre-existing conduction disorders, neither did it provoke new disturbances of this type in any of the remaining 15 patients.

SERUM CONCENTRATIONS OF AMIODARONE AND DESETHYL AMIODARONE CONCENTRATION (figure 1)

In three patients the serum concentrations of amiodarone and desethyl amiodarone were measured immediately before and after the short term infusion. They were also measured every two hours during the 24 hour intravenous treatment. Serum concentrations of amiodarone reached an initial peak of between 4·9 and 7·8 µg/ml immediately after the short term infusion. During the succeeding period of observation they ranged from 0·5 to 1·5 g/ml. Concentrations of desethyl amiodarone, however, behaved differently. In one patient this metabolite was found four hours after treatment started, but in the remaining two it was never detected during the intravenous infusion.

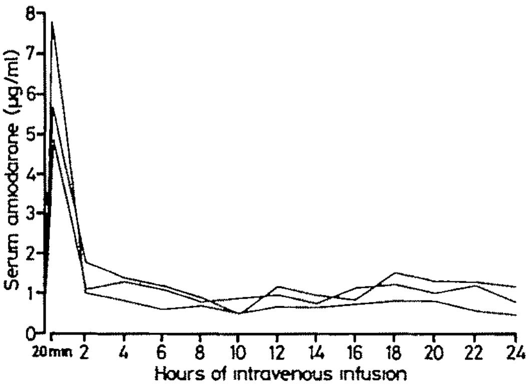


Figure *Time course of serum amiodarone concentration during intravenous amiodarone infusion in three patients. Note the peak immediately after the short term infusion and the nearly constant blood concentrations from the second to the twenty fourth hour.*

Table 3 *Electrocardiographic effects of the amiodarone infusion (mean (1 SD))*

Interval	*Control (ms)*	*Intravenous amiodarone (ms)*
RR	741 (206)	713 (178)
PR	180 (40)	185 (33)
QRS	99 (16)	102 (1)
QTc	462 (65)	467 (53)

There were no significant differences between the control and amiodarone results.

Discussion

This study shows that intravenous amiodarone can be used safely and effectively for the short term control of frequent recurrent ventricular tachycardia and ventricular fibrillation and also for the termination of sustained ventricular tachycardia. The rate of termination in our patients—eight out of 19—is lower than the average of 70% in other reports.[7–9] This discrepancy is primarily the result of different rates of amiodarone administration. We started treatment with a short term infusion rather than a bolus, which occasionally results in severe complications.[4] In five patients in whom persistent ventricular tachycardia was rapidly corrected by cardioversion, hypotension occurred during short term infusion of amiodarone. Therefore close supervision and continuous monitoring not only of the electrocardiogram but also of blood pressure are recommended during intravenous amiodarone administration.

Of greater clinical significance than the termination of sustained ventricular tachycardia is the prompt efficacy with which amiodarone prevented ventricular tachycardia and ventricular fibrillation in our patients. Thus intravenous amiodarone on its own controlled tachycardia in nine of the 15 patients with frequent attacks of ventricular tachycardia or ventricular fibrillation that were refractory to other antiarrhythmic drugs. In addition three further patients were stabilised by supplementary administration of a previously ineffective antiarrhythmic drug and ventricular pacing. Similar positive results were also reported by Morady *et al*, who treated their patients mainly by repeating a bolus,[10] and by Saksena *et al*, who performed continuous infusions for 4–7 days.[11] Blood concentrations of amiodarone at the dosage we chose tend to be at the lower end of the range generally regarded as therapeutically effective. Therefore an increase of the dose infused over 24 hours might be expected to lead to better results, especially in patients with frequent attacks.

Only occasionally during the treatment with intravenous amiodarone did serious side effects occur that required the treatment to be stopped or the application of additional measures. The augmentation of the arrhythmias seen in one patient started 30 minutes after the start of treatment and persisted for about an hour after interruption of the infusion. This arrhythmogenic effect was not accompanied by a QTc prolongation, although such a correlation has been reported during oral amiodarone.[12 13] During the sinus arrest which occurred after cardioversion a supraventricular escape rhythm and a fall in blood pressure were seen. The immediate intravenous administration of 1 mg atropine resulted in rapid restoration of sinus rhythm and normalisation of blood pressure. A few weeks before this patient showed normal sinus node function in a follow up electrophysiological study. Although a sinus arrest was reported to have been induced by intravenous amiodarone in one instance, the cause of the arrest in our case cannot be clearly attributed to the drug, because bradycardia seems to occur in 25% of all ventricular arrhythmias treated by cardioversion.[14 15]

All our patients showed depressed left ventricular function and some of them had severe congestive heart failure. Nevertheless we never saw a lasting deterioration of cardiac output. Others had confirmed that intravenous amiodarone is well tolerated provided bolus doses are avoided.[10 11] In our patients we found no alterations in the surface electrocardiogram during the 24 hour infusion of amiodarone. This observation was also reported by Wellens *et al*.[16] But Saksena *et al* found a prolongation of the RR, PR, QRS, and QTc intervals.[11] Because their infusion lasted 4–7 days, these changes are likely to be typical type III effects like those produced by long term oral administration. In long term oral treatment there is a correlation between antiarrhythmic action and QTc prolongation.[17 18] Because a QTc prolongation cannot be detected during short term intravenous amiodarone administration, the short term effect in intravenous administration seems to be based upon the inhibition of the rapid inward sodium current, which was shown especially during acute superfusion with the drug in previously untreated papillary muscles by Mason *et al*.[19] An effect of amiodarone on the rapid inward sodium current was also suggested earlier by Coumel and Bouvrain[20] and Surawicz.[21]

Neither the short term infusion nor the subsequent 24 hour intravenous administration of amiodarone led to a deterioration of the atrioventricular or intraventricular conduction in any of our patients. This also held true when there was a pre-existing conduction disorder. Because of the effect of the drug on the atrioventricular node it should only be given after insertion of a pacemaker lead in patients with atrioventricular block.

LIMITATIONS OF THE STUDY

Because amiodarone was administered intravenously in all 26 patients we are not able to make a statement about the efficacy of this drug compared with that of other intravenously administered antiarrhythmics. A controlled comparative study, however, is impracticable because it would not be acceptable to stop a successful treatment in critically ill patients. Because all 26 patients were treated with other antiarrhythmic agents until just before the start of intravenous treatment, an additive effect cannot be ruled out. None the less, these antiarrhythmic agents were not effective when administered alone.

Intravenous amiodarone treatment with the specified dosage is effective both in the termination of sustained ventricular tachycardia and in the acute control of frequently recurring ventricular tachycardia and ventricular fibrillation that are refractory to treatment with other antiarrhythmic agents. With appropriate monitoring intravenous amiodarone can be used safely even in patients with left ventricular dysfunction and intraventricular conduction disturbances.

References

1 Morady F, Sauve MJ, Malone P, *et al*. Long-term efficacy and toxicity of high-dose amiodarone therapy for ventricular tachycardia or ventricular fibrillation. *Am J Cardiol* 1983;52:975–9.

2 McGovern B, Garan H, Malacoff RF, *et al*. Long-term clinical outcome of ventricular tachycardia or fibrillation treated with amiodarone. *Am J Cardiol* 1984;53: 1558–63.

3 Heger JJ, Prystowsky EN, Zipes DP. Clinical efficacy of amiodarone in treatment of recurrent ventricular tachycardia and ventricular fibrillation. *Am Heart J*

1983;**106**:887–94.

4 Marens FJ, Fontaine GH, Frank R, Grosgogeat Y. Clinical pharmacology and therapeutic applications of the antiarrhythmic agent amiodarone. *Am Heart J* 1981;**101**:480–93.

5 Holt P, Crick JCP, Davies DW, Curry P. Intravenous amiodarone in the acute termination of supraventricular arrhythmias. *Int J Cardiol* 1985;**8**:67–76.

6 Faniel R, Schoenfeld P. Efficacy of i.v. amiodarone in converting rapid atrial fibrillation and flutter to sinus rhythm in intensive care patients. *Eur Heart J* 1983; **4**:180–5.

7 Benaim R, Uzan C. Les effets antiarhythmiques de l'amiodarone injectable (a propos de 153 cas). *Rev Med* 1978;**19**:1959–63.

8 Fauchier JP, Brochier M, Raynaud R. Etude clinique des effets antiarhythmiques ventriculaires de l'amiodarone (orale et injectable). *Ann Cardiol Angeiol* 1973;**22**:427–35.

9 Michat L, Cabrol C, Cabrol A, *et al.* Effets antiarhythmiques de l'amiodarone injectable en reanimation de chirurgie cardiovasculaire [Letter]. *Nouv Presse Med* 1976;**5**:1996.

10 Morady F, Schienman MM, Shen E, Shapiro W, Sung RJ, Di Carlo L. Intravenous amiodarone in the acute treatment of recurrent symptomatic ventricular tachycardia. *Am J Cardiol* 1983;**51**:156–9.

11 Saksena S, Rothbart ST, Shah Y, Capello G. Clinical efficacy and electropharmacology of continuous intravenous amiodarone and chronic oral amiodarone in refractory ventricular tachycardia. *Am J Cardiol* 1984;**54**:347–52.

12 McGovern B, Garan H, Kelly E, Ruskin F. Adverse reactions during treatment with amiodarone hydrochloride. *Br Med J* 1983;**287**:175–80.

13 Leory G, Haiat R, Barthelemy M, Lionnet F. Torsade de pointes during loading with amiodarone. *Eur Heart J* 1987;**8**:541–3.

14 Veltri EP, Reid Ph R. Sinus arrest with intravenous amiodarone. *Am J Cardiol* 1986;**58**:1110–1.

15 Eysmann SB, Marchlinski FE, Buxton AE, Josephson ME. Electrocardiographic changes after cardioversion of ventricular arrhythmias. *Circulation* 1986; **73**:73–81.

16 Wellens HJJ, Brugada P, Abdollah H, Dassen WR. A comparison of the electrophysiologic effects of intravenous and oral amiodarone in the same patient. *Circulation* 1984;**69**:120–4.

17 Nademanee K, Hendrickson JA, Cannon OS, Goldreyer BN, Singh BN. Control of life-threatening ventricular tachyarrhythmias by amiodarone. *Am Heart J* 1981;**101**:759–68.

18 Singh BN, Nademanee K, Kannan R, Ikeda N. The clinical results of amiodarone in cardiac arrhythmias: optimal dosing. *PACE* 1984;**7**:109–24.

19 Mason JW, Hondeghem LM, Katzung BG. Block of inactivated sodium channels and of depolarization—induced automatically in guinea pig papillary muscle by amiodarone. *Circ Res* 1984;**55**:277–85.

20 Coumel P, Bouvrain Y. Etude clinique des effets pharmacodynamiques et antiarythmiques de l'amiodarone. *J Agrégés* 1972;**6**:69–81.

21 Surawicz B. What protects the heart from standstill and fibrillation? In: Russek HI, ed. *The Paul D. White symposium on cardiovascular disease*. Baltimore: Williams and Wilkins, 1973:320–34.

Br Heart J 1989;**62**:372–8

Inaccuracies in using aortic valve gradients alone to grade severity of aortic stenosis

M J GRIFFITH,* CATHERINE CAREY,† D J COLTART, B S JENKINS,
M M WEBB-PEPLOE

From the Department of Cardiology, St Thomas' Hospital, London

SUMMARY The severity of aortic stenosis is an important determinant of prognosis in patients with symptoms who do not undergo valve replacement. To assess the pitfalls of using valve gradients alone 636 patients with aortic stenosis in whom the aortic valve area had been calculated by the Gorlin formula were studied. The correlation between valve area and aortic gradients was poor. No gradient was found that was both sensitive and specific for aortic stenosis. The maximum predictive accuracy was 81% for a mean gradient of 30 mm Hg and 80% for a peak gradient of 30 mm Hg. A mean gradient of 50 mm Hg or a peak gradient of 60 mm Hg were specific with a 90% or more positive predictive value. It proved difficult, however, to find a lower limit with a 90% negative predictive value. Patients with severe aortic stenosis and low gradients (peak or mean gradient of < 30 mm Hg) had small ventricles (on both angiographic and echocardiographic data) with good ejection fractions and so were unlikely to be detected subjectively. In comparison patients with mild aortic stenosis and low gradients tended to have more aortic regurgitation but have similar degrees of left ventricular hypertrophy on echocardiographic or electrocardiographic criteria.

The aortic valve area should be measured in all patients with the suspicion of severe aortic stenosis with a mean gradient of < 50 mm Hg (50% of patients in this study) or a peak gradient of < 60 mm Hg (47% of patients in this study).

The severity of aortic stenosis, as assessed by valve area, is an important determinant of prognosis in patients with symptoms who do not undergo valve replacement.[1] The widespread use of aortic valve gradients alone, either derived invasively or by Doppler echocardiography, is likely to be an inaccurate way of assessing the severity because it ignores cardiac output. This inaccuracy is increased by the fall in cardiac output as aortic stenosis progresses.[2-4] Furthermore, patients with low cardiac outputs have a very poor short term prognosis if the valve is not replaced.[5]

We studied the inaccuracy of both mean and peak aortic valve gradients alone in predicting aortic valve area and the values of valve gradient at which valve area must be calculated to ensure accurate assessment of the severity of aortic stenosis.

Patients and methods

METHODS

Over a 10 year period 636 consecutive patients with a precatherisation diagnosis of aortic stenosis were studied at St Thomas' Hospital. Patients were catheterised if they had symptoms or if the clinical diagnosis of severe aortic stenosis was made. Because Doppler assessment of the gradient or valve area was not available (or in its development phase), no attempt was made to grade the severity on the basis of the echocardiogram. All patients underwent full left and right heart catheterisation. All had an aortic valve gradient > 10 mm Hg. Patients with mitral stenosis or > grade I mitral regurgitation were excluded from the study. Cardiac output was calculated by indocyanine green dye dilution. Dye was injected in the pulmonary artery and measurement was made with an earpiece densitometer and dye curve analysis was performed by a Nihon Kohden cardiac output computer.[6] This was verified by the fore-'n-aft triangle method.[7] The mean of three measurements was calculated.

Requests for reprints to Dr M J Griffith, St George's Hospital, London SW17 0RE.

Present addresses *St George's Hospital, London SW17 0RE; †The London Hospital, London E1 1BB

Accepted for publication 23 May 1989

Angiographic volumes were measured by planimetry from the right anterior oblique angiogram.[8] Intracardiac distances were calibrated by moving the angio table a known distance and using the tip of the pigtail catheter in the left ventricle as the reference point. Extrasystolic or post-extrasystolic beats were excluded and angiographic stroke volume and cardiac output were then calculated by planimetry. The aortic valve gradient was measured by withdrawal of a fluid filled catheter across the valve. In atrial fibrillation simultaneous measurements were obtained with twin lumen catheters and the transseptal approach was used when the aortic valve could not be crossed retrogradely. Peak to peak gradients were measured directly and the mean gradient was measured by computerised planimetric integration, averaged over a minimum of five beats. The systolic ejection period was calculated in the standard manner. The aortic valve area was then calculated with the classic Gorlin formula[9] based on the green dye cardiac output, unless there was grade 3 or 4 aortic regurgitation, when the angiographic cardiac output was used.

$$\text{Aortic valve area (cm}^2\text{)} = \frac{\text{valve flow (ml/min)}}{44{\cdot}5\ \text{mean valve gradient}}$$

Electrocardiographic left ventricular hypertrophy was defined as being present if the sum of the S wave in lead V1 and the R wave in lead V5 or V6 was >35 mm.[10]

One operator performed and reported 90% of the echocardiograms. The M mode was guided by cross sectional images, using the ATL 300 or the Hewlett-Packard 7702A machines. The echocardiographic dimensions of the wall and cavity were measured just below the tips of the mitral valve leaflets in the parasternal view. Wall dimensions were measured at the end of diastole.

STATISTICAL ANALYSIS

Log plots of mean and peak gradients were plotted against the aortic valve area to determine the correlation coefficient. We used logarithmic plots because the relation is not linear. Because of the possibility that lack of correlation was a function of aortic regurgitation this was repeated with the patients divided into subgroups by angiographic grade of aortic regurgitation. Severe aortic stenosis was defined as a valve area of $\leqslant 0{\cdot}9$ cm^2 and the sensitivity, specificity, and diagnostic accuracy were calculated for the range of values of aortic valve gradients. Both these functions were performed on the University of London computer by the Statistical Analysis System. Student's *t* test was used to compare continuous variables and χ^2 was used for proportions.

Table 1 *Patient details*

Variable	*Result*
Sex	29% female
Mean (SD) age	58 (11) yr
Mean valve area	0 94 (0·71) cm^2
Peak gradient	60·3 (35) mm Hg
Mean gradient	50·6 (25) mm Hg
Mean EF	57 (15)%
Mean CI	3 3 (1 6) l/min/m^2
Mean LVEDI	95 1 (45) ml/m^2

EF, angiographic ejection fraction; CI, cardiac index; LVEDI, angiographic left ventricular volume index.

Results

Table 1 summarises the patient details. The aortic valve area was calculated in all patients and the peak gradient was available in 597 patients. The patient population studied had a range of severity of aortic stenosis with a mean aortic valve area of 0·94 cm^2. Table 2 shows the details of the patients' symptoms. Nearly all the patients had symptoms (94%)—with chest pain in 58% and syncope in 23%. The patients with severe aortic stenosis were significantly more likely to have symptoms and specifically more likely to have chest pain or syncope than those patients with mild aortic stenosis. Figures 1 and 2 show the plots of aortic valve area against mean and peak gradients and figs 3 and 4 show the log plots. There is a wide degree of scatter and this is reflected in the poor correlation seen with r values of $-0{\cdot}71$ and $-0{\cdot}70$ for mean and peak gradients respectively calculated by linear regression from the logarithmic plots. There was little difference when the patients were subdivided according to grade of aortic regurgitation (table 3). When there was no aortic regurgitation the r value reached $-0{\cdot}78$ for the mean gradient.

Table 4 examines the effect of age on the correlation. There was little difference between the various age groups except in the patients aged >70 in whom the correlation was much poorer (0·53 for mean gradients and 0·43 for peak gradients).

Tables 5 and 6 show the sensitivity and specificity of aortic valve gradients from 20 to 100 mm Hg for peak gradients and mean gradients respectively. The maximum predictive accuracy is 81% for a mean

Table 2 *Patients' symptoms in relation to severity of aortic stenosis*

Symptoms	*Severe stenosis*	*Mild stenosis*
None	15/443 (3%)	25/217 (12%)
Chest pain	274/443 (62%)*	108/217 (50%)*
Syncope	129/443 (29%)*	27/217 (12%)*

*p < 0 01

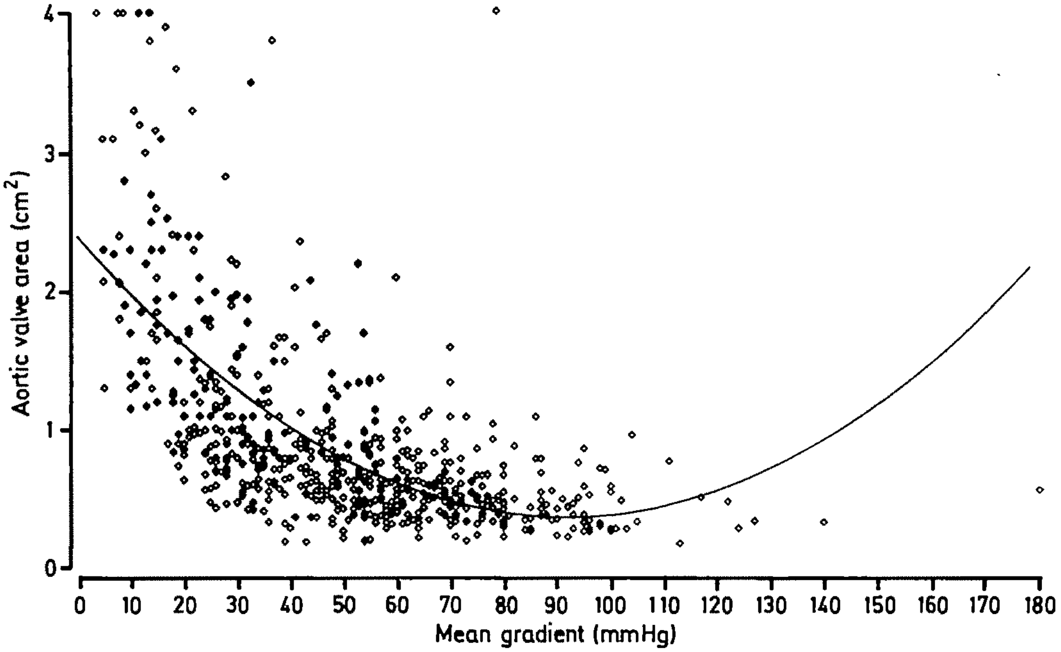


Fig 1 *A plot of aortic valve area against mean gradient gave a quadratic regression line.*

gradient of 30 mm Hg and 80% for a peak gradient of 30 mm Hg.

We hoped to establish a range of highly specific or sensitive gradients for clinical use—the upper limit with a 90% positive predictive value and the lower limit with a 90% negative predictive value. A peak gradient of 60 mm Hg and a mean gradient of 50 mm Hg were used as the upper limits. It proved

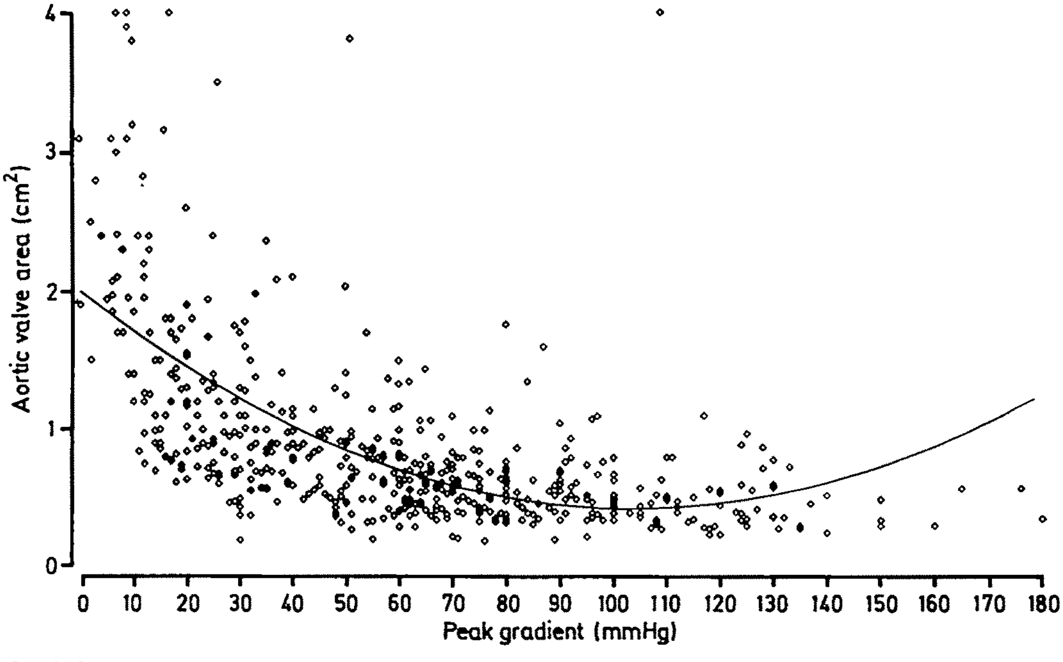


Fig 2 *A plot of aortic valve area against peak gradient gave a quadratic regression line.*

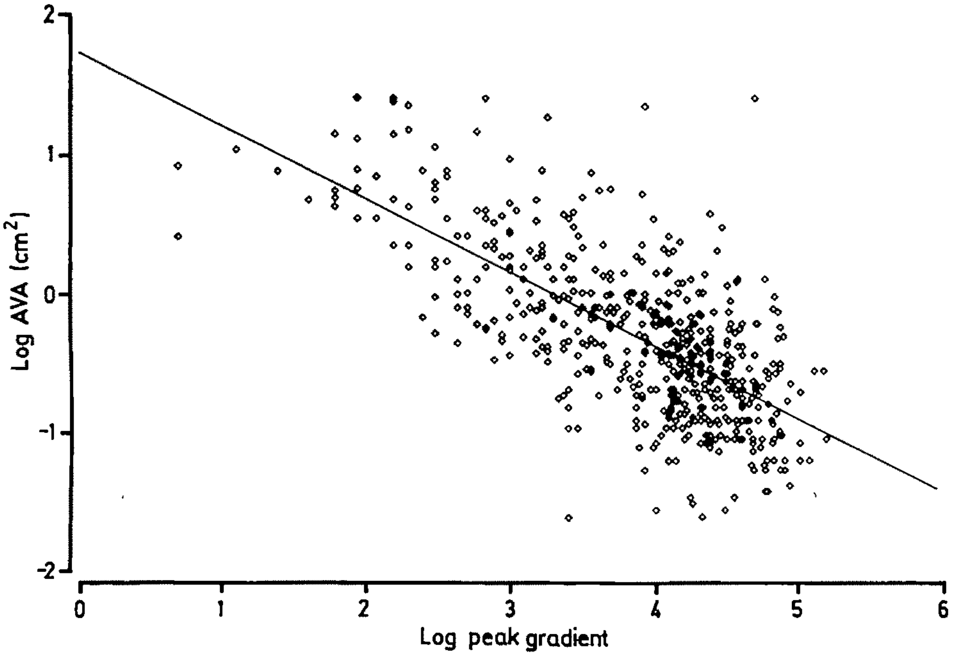


Fig 3 *A plot of the natural logarithm of aortic valve area against the peak aortic valve gradient gave a linear regression line.*

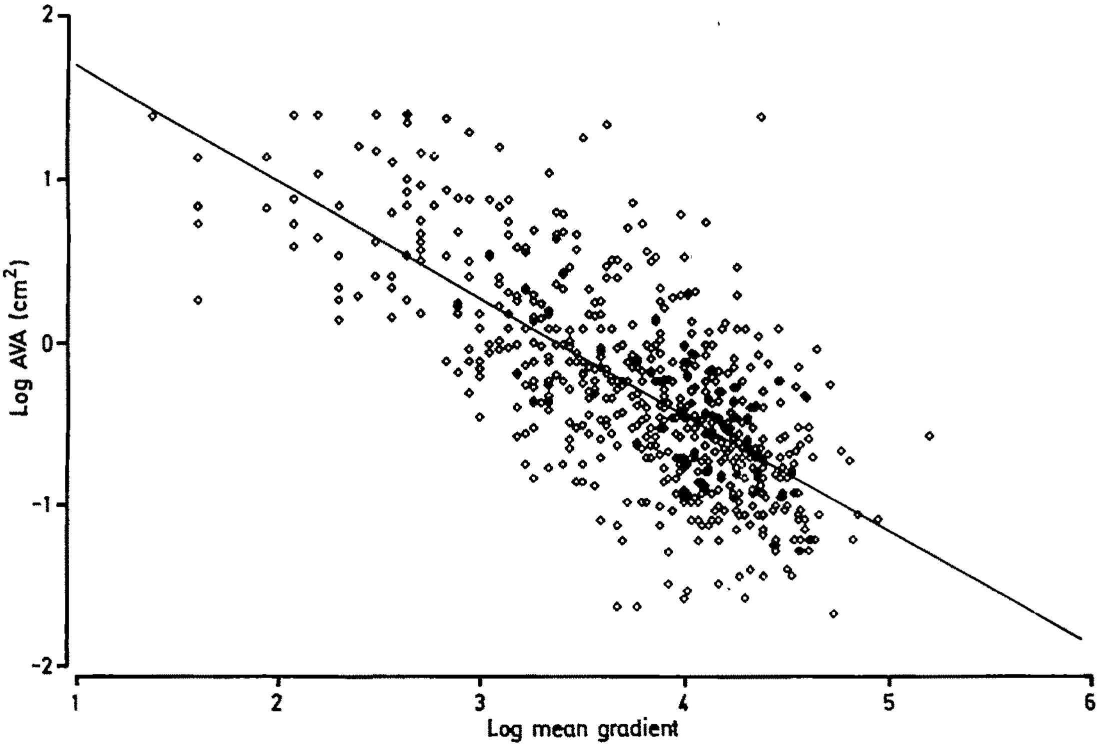


Fig 4 *A plot of the logarithm aortic valve area against mean aortic valve gradient gave a linear regression line.*

Table 3 *Correlation coefficients for the logarithmic plots of mean and peak gradients and valve area by angiographic grade of aortic regurgitation*

Grade AR	*Aortic valve gradient*		*Number**
	Peak	*Mean*	
0	−0·73	−0·78	72
1	−0·63	−0·68	270
2	−0·68	−0·66	189
3	−0·69	−0·69	97
4	−0·63	−0·68	7
All	−0·70	−0·71	636

AR, angiographic grade of aortic regurgitation
*Number of patients with that grade of aortic regurgitation.

Table 4 *Correlation coefficients for the logarithmic plots of mean and peak gradients and valve area by age group of patients*

Age (yr)	*Aortic valve gradient*		*Number*
	Peak	*Mean*	
<40	0·64	0·64	47
40–49	0·76	0·76	87
50–59	0·69	0·70	176
60–69	0·72	0·73	262
>70	0·53	0·53	88

difficult to define a lower limit that correctly classified a reasonable number of patients, so we used both 20 mm Hg and 30 mm Hg for the mean and peak gradients. With these criteria 12% of patients with a mean gradient <20 mm Hg and 18% of patients with a peak gradient of <20 mm Hg would be misclassified as having mild aortic stenosis. The figures increased to 23% and 30% respectively when a lower limit of 30 mm Hg was used. These patients were looked at in more detail (see table 7). As expected, these patients with low gradients and severe stenosis had low cardiac indices and usually had little or no aortic regurgitation, but their ejection fractions were normal with normal end diastolic volume indices. The ejection fractions were in fact better than in those patients with mean or peak gradients <20 mm Hg and mild stenosis but the misclassified patients had significantly smaller ventricles by angiographic or echocardiographic estimation ($p < 0.05$). The patients with severe stenosis had less aortic regurgitation. There was no significant difference in left ventricular hypertrophy when determined by either echocardiographic wall dimensions or on electrocardiographic criteria, though there was a trend for patients with mild aortic stenosis to have more electrocardiographic left ven-

Table 5 *Power of peak aortic valve gradients to predict severe aortic stenosis (aortic valve area <0·9 cm²) in 569 patients*

Gradient (mm Hg)	*Specificity (%)*	*Sensitivity (%)*	*Predictive value*		*Accuracy (%)*	*Number of patients**
			+ve (%)	*−ve (%)*		
< 20						89
> 20	42	96	79	82	80	56
> 30	59	89	83	70	80	55
> 40	72	81	86	62	78	38
> 50	78	74	88	57	76	58
> 60	88	64	92	51	71	69
> 70	92	48	93	44	71	60
> 80	95	34	93	38	53	29
> 90	96	27	94	37	48	41
>100	98	18	96	34	42	74

*Patients with gradients ⩾10 mm Hg.

Table 6 *Power of mean aortic valve gradients to predict severe aortic stenosis (aortic valve area <0·9 cm²) in 636 patients*

Gradient (mm Hg)	*Specificity (%)*	*Sensitivity (%)*	*Predictive value*		*Accuracy (%)*	*Number of patients**
			+ve (%)	*−ve (%)*		
< 20						77
> 20	33	98	75	88	77	82
> 30	60	92	83	77	81	79
> 40	73	80	86	63	77	83
> 50	84	66	90	54	72	101
> 60	93	46	93	45	61	81
> 70	97	30	95	40	51	67
> 80	99	15	97	36	42	26
> 90	100	9	98	34	38	27
>100	100	3	100	33	34	13

*Number of patients with gradients ⩾10 mm Hg.

Table 7 *Details of patients misclassified when gradients with a 90% predictive accuracy were used*

Gradient	*Number*	*CI (l/min/m^2)*	*AR > 1*	*EF (cm^3/m^2)*	*EDVI*	*LVED (cm)*	*Septum (cm)*	*PW (cm)*	*LVH (%)*
All:									
Mild	217/660	4·6	72%	58%	116	6·0	1·27	1·14	45
Severe	443/660	2·7**	35%**	57%	86**	5·3	1·38*	1·20**	50
Mean < 20 mm Hg:									
Mild	68/ 77 (78%)	4·1	50/ 68 (73%)	53%	126	6·5	1·22	1·03	48
Severe	9/ 77 (12%)	2·4**	2/ 9 (22%)**	58%	81*	5·5	1·30	1·12	50
Mean > 50 mm Hg:									
Mild	31/315 (10%)	5·9	29/ 31 (94%)	61%	118	5·7	1·39	1·20	47
Severe	284/315 (90%)	2·8**	109/284 (39%)**	58%	83**	5·14*	1·42	1·26	53
Mean < 30 mm Hg:									
Mild	123/159 (77%)	4·1	81/123 (67%)	55%	118	6·3	1·22	1·09	45
Severe	36/159 (23%)	2·2**	6/ 36 (17%)**	57%	85**	5·3**	1·30	1·12	23*
Peak < 20 mm Hg:									
Mild	73/ 89 (82%)	4·3	56/ 73 (77%)	56%	118	6·3	1·25	1·13	43
Severe	16/ 89 (18%)	2·3**	1/ 16 (6%)**	62%	80*	4·9**	1·18	1·07	20
Peak > 60 mm Hg:									
Mild	20/273 (7%)	5·7	16/ 20 (80%)	63%	110	5·4	1·38	1·18	50
Severe	253/273 (93%)	2·8**	100/253 (40%)**	57%	83**	5·1	1·42	1·26	52
Peak < 30 mm Hg:									
Mild	102/145	4·2	74/102 (73%)	57%	116	6·1	1·26	1·13	44
Severe	43/145 (%)	2·3**	7/ 35 (14%)**	58%	84*	5·2**	1·27	1·12	29

This table shows in detail the patients who would be misclassified if gradients alone were used to grade the severity of aortic stenosis. The gradients used are the minimum gradient that had a >90% positive predictive value for severe aortic stenosis and the maximum gradient that had a >90% positive predictive value for mild aortic stenosis for both mean and peak gradients. Because no single gradient gave a predictive accuracy of >90% for mild aortic stenosis we used two gradients (20 mm Hg and 30 mm Hg).

CI, cardiac index, AR > 1 = number of patients with greater than angiographic grade 1 aortic regurgitation; EF, angiographic ejection fraction; EDVI, angiographic end diastolic volume index; mild, aortic valve area >0·9 cm^2, severe, aortic valve area ⩽0·9 cm^2.

*p < 0·05 and **p < 0·01 for comparisons between mild and severe stenosis.

tricular hypertrophy. This difference was significant for mean gradients of <30 mm Hg. At <30 mm Hg, the peak gradient is more likely to underestimate severity. Body surface area was the same in the two groups.

The higher gradients were more useful because they gave a much lower level of misclassification (10% for a mean gradient of >50 mm Hg and 7% with a peak gradient of >60 mm Hg). Furthermore, most (94% and 78%) of these patients had >grade 1 aortic regurgitation. The ejection fraction was similar to that in patients with severe aortic stenosis but again these patients had significantly smaller ventricles and there was no difference in echocardiographic wall dimensions or electrocardiographic left ventricular hypertrophy.

Of the patients studied 36% and 38% respectively had intermediate gradients that were neither sensitive or specific enough to be used on their own (peak from 20–60 mm Hg, mean from 20–50 mm Hg).

Discussion

An objective measure of the severity of aortic stenosis is important as it is on this basis that the decision for aortic valve replacement is made. If the valve area is accepted as the best measure available then this study shows the inadequacy of using aortic valve gradients alone. Haemodynamic studies of prognosis in severe aortic stenosis have been limited because the effectiveness of aortic valve replacement was demonstrated before modern haemodynamic methods were available.[11–13] The recent study by Turina and colleagues in patients who refused operation showed that prognosis was best predicted by the valve area.[1] Patients with symptoms and a valve area of <0·9 cm^2 had a poor prognosis while those with a larger valve area with or without symptoms had a good prognosis. Symptom free patients did not have the same poor prognosis; this result is further supported by the study by Kelly and colleagues who found no difference in mortality (excluding the perioperative period) between unoperated patients without symptoms and patients with similar valve areas who had undergone valve replacement.[14] The importance of the cardiac output was shown by Matthews and colleagues who found that patients with poor left ventricular function and low cardiac output were more likely to die while awaiting valve replacement.[5] Furthermore, because serial haemodynamic studies showed that as aortic valve disease progresses the cardiac output falls, the use of the gradient alone will underestimate the degree of progression.[2-4] It may be argued that cardiac output is included because even where the valve area is not formally calculated, the decision to operate is also based on the subjective angiographic, echocardiographic, or clinical appearance and is not based on the gradient alone. This study showed that in patients with low gradients those with severe aortic stenosis had similar (or slightly better) ejection fractions and significantly smaller ventricles than those with mild aortic stenosis. These patients would be very difficult to identify on the subjective appearance of the echocardiogram or angiogram and would only be identified if the cardiac output was formally measured. The traditional clues of echocardiographic or electrocardiographic left ventricular hypertrophy would not be helpful because there is no significant difference between patients with severe and mild stenosis and low gradients. The patients with high gradients and mild aortic stenosis nearly all had grade 2 or more aortic regurgitation with large ventricles with good ejection fractions and would be less difficult to identify. In any case, the combination of stenosis and regurgitation in these patients may be sufficient to recommend operation.

It seems illogical to mix objective and subjective measurements when objective evidence can be obtained easily, either invasively or non-invasively. Doppler measurement of the aortic valve area by either the Gorlin formula or a continuity equation correlated closely with invasive measurements.[15-17] Doppler gradients alone, however, are poor predictors of valve area; the study by Danielsen and colleagues produced very similar correlations to our study.[18]

We suggest the following guidelines for calculating valve areas if a selective policy is envisaged. An upper limit of a mean gradient of 50 mm Hg or a peak gradient of 60 mm Hg will have a low false positive rate for severe aortic stenosis and most of these patients will have clinically significant aortic regurgitation. We cannot, however, stake an effective lower limit because false negative rates were high for gradients of 20 or 30 mm Hg, especially where the peak gradient was used. These patients would be difficult to identify if the valve area is not calculated because they have relatively small ventricles with good ejection fractions. We therefore recommend that the aortic valve area should be calculated in all patients with symptoms and aortic stenosis with a mean gradient of <50 mm Hg (50% of patients in this study) or a peak gradient of <60 mm Hg (47% of patients in this study), particularly if there is no aortic regurgitation.

References

1 Turina J, Hess O, Sepulcri F, Krayenbuehl HP. Spontaneous course of aortic valve disease. *Eur Heart J* 1987;**8**:471–83.

2 Wagner S, Selzer A. Patterns of progression of aortic stenosis: a longitudinal haemodynamic study. *Circulation* 1982;**65**:709–12.

3 Nestico PF, DePace NL, Kimbiris D, *et al.* Progression of isolated aortic stenosis: analysis of 29 patients having more than one cardiac catheterization. *Am J Cardiol* 1983;**52**:1054–8.

4 Bogart DB, Murphy BL, Wong BYS, Pugh DM, Dunn MI. Progression of aortic stenosis. *Chest* 1979;**76**: 391–6.

5 Matthews AW, Barritt DW, Keen GE, Belsey RH. Preoperative mortality in aortic stenosis. *Br Heart J* 1974;**36**:101–3.

6 Robinson PS, Crowther A, Jenkins BS, Webb-Peploe MM, Coltart DJ. A computerized dichromatic earpiece densitometer for the measurement of cardiac output. *Cardiovasc Res* 1979;**13**:420–6.

7 Bradley EC, Barr JW. Fore-'n-aft triangle formula for rapid estimation of area. *Am Heart J* 1969;**78**:643–8.

8 Greene DG, Carlisle R, Grant C, Bunnell IL. Estimation of left ventricular volume by one plane cineangiography. *Circulation* 1967;**35**:61–9.

9 Gorlin R, Gorlin SG. Hydraulic formula for the calculation of the area of the stenotic mitral valve, other cardiac valves, and central circulatory shunts. *Am Heart J* 1951;**41**:1–29.

10 Romhilt DW, Estes EH. Point-score system for the ECG diagnosis of left ventricular hypertrophy. *Am Heart J* 1968;**75**:752–8.

11 Takeda J, Warren R, Holzman D. Prognosis of aortic stenosis. Special reference to indications for operative treatment. *Arch Surg* 1963;**87**:931–6.

12 Frank S, Johnson A, Ross J Jr. Natural history of valvular aortic stenosis. *Br Heart J* 1973;**35**:41–6.

13 Ross J, Braunwauld E. Aortic stenosis. *Circulation* 1968;**38**:V61–7.

14 Kelly TA, Rothbart RM, Cooper CM, Kaiser DL, Smucker ML, Gibson RS. Comparison of outcome of asymptomatic to symptomatic patients older than 20 years of age with valvular aortic stenosis. *Am J Cardiol* 1988;**61**:123–30.

15 Zoghbi WA, Farmer KL, Soto JG, Nelson GN, Quinones MA. Accurate noninvasive quantification of stenotic aortic valve area by Doppler echocardiography. *Circulation* 1986;73:452–9.

16 Ohlsson J, Wranne B. Noninvasive assessment of valve area in patients with aortic stenosis. *J Am Coll Cardiol* 1986;7:501–8.

17 Otto KM, Pearlman AS, Comess KA, Reamer RP, Janko CL, Huntsman LL. Determination of the stenotic valve area in adults using Doppler echocardiography. *J Am Coll Cardiol* 1986;7:509–17.

18 Danielsen R, Nordrehaug JE, Stangeland L, Vik-Mo H. Limitations in assessing the severity of aortic stenosis by Doppler gradients. *Br Heart J* 1988;**59**: 551–5.

Br Heart J 1989;**62**:379–383

HLA antigens in idiopathic dilated cardiomyopathy

CONSTANTINOS J LIMAS, CATHERINE LIMAS

From the Departments of Medicine (Cardiovascular Section) and Laboratory Medicine and Pathology, University of Minnesota School of Medicine, Minneapolis, Minnesota, USA

SUMMARY Disturbances of humoral and cellular immunity are common in patients with idiopathic dilated cardiomyopathy and they may contribute to the initiation and maintenance of myocardial damage. HLA antigens were studied in 102 patients with dilated cardiomyopathy and a control hospital population. HLA-DR4 was significantly more common in patients with idiopathic cardiomyopathy (41 patients, 40%) than in the control group (123 patients, 24%). The distribution of other antigens was not significantly different in the two groups. The distribution of blood group antigens, immunoglobulin concentrations, and disease severity was similar in patients with the HLA-DR4 antigen and those without it.

These results suggest that HLA-DR4 antigen may be a genetic marker for susceptibility to dilated cardiomyopathy.

Idiopathic dilated cardiomyopathy is a clinical entity of unknown and probably heterogeneous aetiology. In the search for pathogenetic mechanisms, considerable attention has been focused on the possibility that disturbed immunity may be important.[1-9] Several abnormalities in cellular[1-5] and humoral[6-9] immunity have already been described in patients with idiopathic dilated cardiomyopathy and are thought to be triggered by an initial episode of myocardial damage (for example after viral infection) that sets the stage for an autoimmune response. Development of autoimmunity is the summation of diverse genetic traits that give rise to a genetic predisposition expressed both as an increased susceptibility to infectious (for example viral) agents and to organ specific autoimmune reactions.[10]

In most reported cases a predisposition to autoimmune disease is under the control of immune response genes[10 11] and as a result autoimmune disorders show preferential associations with the products of immunoglobulin, complement, or HLA genes. For example, there is a significant increase in the frequency of HLA-B27 antigens in ankylosing spondylitis, HLA-DR3/DR4 in juvenile diabetes mellitus, and HLA-DR3 in myasthenia gravis (for a review, see Tiwari and Terasaki[12]). Furthermore, expression of class II HLA genes is thought to be of overriding importance in the presentation of self-antigens that leads to the pathological manifestations of organ-specific autoimmunity.[13] Such expression may be induced in response to viral infection or as a result of the initial tissue damage induced by the putative initiating agent. To examine the possible role of immune response factors in the pathogenesis of idiopathic dilated cardiomyopathy, we compared the frequency of histocompatibility antigens A, B, C, and DR with that expected in a control population.

Patients and methods

We studied 102 white patients (aged 16–65, mean (SD) 43·8 (10)) with idiopathic dilated cardiomyopathy; none was alcoholic. There were 18 (17·6%) women. About 90% of these patients were of Northern European (predominantly Scandinavian) origin. Cardiac symptoms had been present for 3·51 (1·0) years. There were no diseases known to be associated with specific HLA antigens (such as diabetes mellitus, ankylosing spondylitis, Graves' disease, myasthenia gravis, or rheumatoid arthritis). The severity of myocardial dysfunction in these patients was indicated by a low ejection fraction (20·5 (4%), raised pulmonary capillary wedge pressure (26·8 (5) mm Hg), low cardiac index (2·1 (0·2) l/min/m^2), and high concentrations of plasma noradrenaline 3·4 (0·4) nmol/l). We selected controls for this patient group from a local hospital population. Six hundred and seventeen individuals were typed for HLA A, B, and C loci and 511 for HLA-DR loci (mean age 48 (9) years and 316 (28%) were women).

Lymphocytes for HLA antigen typing were

Requests for reprints to Dr Constantinos J Limas, Department of Medicine, Box 19, UMHC, University of Minnesota School of Medicine, Minneapolis, MN 55455, USA.

Accepted for publication 3 July 1989

isolated from 20 ml heparinised blood by Ficoll-Hypaque (Pharmacia) density gradient centrifugation.[14] Purified B lymphocytes for HLA-DR typing were prepared by the method of Danilovs *et al.*[15] Histocompatibility antigens A, B, and C were assayed on lymphocyte suspensions by the microcytotoxicity method[16] while HLA-DR typing was performed in microlymphocytotoxicity assays with prolonged incubation times on isolated B lymphocytes.[17] In two patients, only Class I HLA antigens were tested. The statistical evaluation of the results followed the methods of Svejgaard *et al.*[18] Chi squared 2 × 2 contingency tables were used for comparisons between patient and control groups. Associations based on small numbers were tested by Fisher's exact test. p values were corrected for the number of antigens tested and associations were regarded as significant if $p < 0·05$. Relative risk and aetiological factor were calculated as previously described.[18]

Results

Tables 1–4 give the HLA antigen frequencies for patients with cardiomyopathy and controls. The frequencies of HLA-A and HLA-C were similar in the two populations and indistinguishable from the expected frequencies in North American populations. Among the HLA-B group, only HLA-Bw44 was slightly overrepresented in the cardiomyopathy group (35·3% compared with 23·2% in the controls, p = 0·05). The difference, however, was not statistically significant after correction for the number of antigens tested (p_c = 0·5). On the other hand, HLA-DR4 was found in 41 (40%) of the cardiomyopathy patients compared with 123 (24%) of the controls (p_c = 0·001). The latter association represented a risk association of 2·20 and an aetiological factor of 0·25. There was no clinical or haemodynamic characteristic that distinguished the HLA-DR4 positive patients from the HLA-DR4 negative patients (table 5). Similarly, the distribution of ABO blood groups was not significantly different in the patients (52% were blood group A, 35% were blood group O, and 13% were blood group B). The distribution of ABO blood groups among patients who were HLA-DR4 positive and those who were negative patients was similar. Concentrations of serum immunoglobulins in patients with idiopathic dilated cardiomyopathy were normally distributed (IgG 9·63 (1·40) g/l, IgA 2·36 (0·43) g/l, IgM 1·06 (0·19) g/l, IgE 193·92 (36·0) g/l).

Table 1 *HLA-A antigen frequencies in patients with idiopathic dilated cardiomyopathy (IDC) and in controls*

	IDC (n = 102)		*Controls (n = 617)*	
HLA type	*n*	%	*n*	%
A1	37	36·3	169	27·4
A2	57	55·9	304	49·3
A3	28	27·4	154	25·0
A11	9	8·8	71	11·5
Aw24	18	17·6	120	19·4
A26	6	5·9	50	8·1
A28	10	9·8	51	8·3
A29	4	3·9	27	4·4
Aw30	8	7·8	28	4·5
Aw32	5	4·9	48	7·8

None of the p_c values was significant

Table 2 *HLA-B antigen frequencies in patients with idiopathic dilated cardiomyopathy (IDC) and controls*

	IDC (n = 102)		*Controls (n = 617)*	
HLA type	*n*	%	*n*	%
B7	24	23·5	153	24·8
B8	20	19·6	121	19·6
B13	7	6·9	24	3·9
B14	6	5·9	49	7·9
B27	11	10·8	47	7·6
Bw35	7	6·9	101	16·4
Bw39	4	3·9	26	4·2
Bw44	36	35·3	143	23·2
Bw51	8	7·8	61	9·9
Bw62	17	16·7	67	10·9

None of the p_c values was significant.

Table 3 *HLA-C antigen frequencies in patients with idiopathic dilated cardiomyopathy (IDC) and controls*

	IDC (n = 102)		*Controls (n = 617)*	
HLA type	*n*	%	*n*	%
Cw1	3	2·9	46	7·5
Cw2	7	6·9	60	9·7
Cw3	19	18·6	124	20·1
Cw4	13	13·0	136	22·1
Cw5	7	7·0	72	11·7

None of the p_c values was significant.

Table 4 *HLA-DR antigen frequencies in patients with idiopathic dilated cardiomyopathy (IDC) and controls*

	IDC (n = 102)		*Controls (n = 511)*	
HLA type	*n*	%	*n*	%
DR1	17	17·0	102	20·0
DR2	23	24·0	161	31·5
DR3	31	30·0	118	23·1
DR4	41	40·0*	123	24·0*
DR5	20	20·0	94	18·4
DRw6	22	22·0	102	20·0
DR7	18	18·0	115	22·5
DRw8	4	4·0	17	3·4
DRw9	2	2·0	10	2·0

*p_c = 0·001.

Table 5 *Clinical characteristics (mean (SD)) of patients with idiopathic dilated cardiomyopathy*

	HLA-DR4 (+) (n = 40)		*HLA-DR4 (−) (n = 62)*	
Age (yr)	46	(7)	47	(8)
Sex (F/M)	8/40		10/62	
Duration of symptoms (yr)	3·3	(0·4)	3·4	(0·7)
Ejection fraction (%)	21·0	(1·5)	18·2	(1·6)
Pulmonary capillary wedge pressure (mm Hg)	28·1	(2·1)	27·3	(2·9)
Cardiac index (l/min/m^2)	2·06	(0·20)	1·98	(0·16)
Plasma noradrenaline (nmol/l)	3·53	(0·48)	2·96	(0·49)

Discussion

There is considerable evidence for immunological dysfunction in patients with dilated cardiomyopathy, and abnormalities of both cellular and humoral immunity have been reported. Das *et al*, for example, showed that a large proportion of cardiomyopathy patients had impaired lymphocyte responses to mitogens.[8] In Chagas's disease, cytotoxic T lymphocytes are directed against both the parasite, *Trypanosoma cruzi*, and heart muscle cells.[2] Jacobs *et al* found cell mediated cytotoxicity against cultured myocardial cells in 30% of patients with cardiomyopathy, 24% of those with other forms of heart disease, and 4% of healthy individuals.[3] An abnormality in suppressor T cell function in patients with dilated cardiomyopathy has been suggested[4] but does not seem to be a uniform finding.[5] Although subgroups of cardiomyopathy patients seem to have abnormalities in lymphocyte function, the relation to the pathogenesis of the disease and clinical severity has not been easy to establish.[19]

Abnormalities in humoral immunity have also been implicated in the pathogenesis of dilated cardiomyopathy. Anti-heart antibodies were detected by immunofluorescence[6 8] or the antiglobulin consumption test[7] and the frequency was correlated with the severity of heart failure and the duration of the disease. Circulating antibodies against specific antigenic determinants, such as sarcolemmal proteins,[6] the adenine nucleotide translocator,[9] and the β adrenoceptor[20] were also reported. Although these findings strongly suggest that immunological responses are important in dilated cardiomyopathy, they do not elucidate the relation of these abnormalities to the initiation and maintenance of myocardial dysfunction.

The possible contribution of genetic factors to the immunologically-associated damage in cardiomyopathy has not received adequate attention. It is known, however, that genetic factors have a role in the pathogenesis of dilated cardiomyopathy, as shown by the cases of familial cardiomyopathy,[21] for which both recessive and dominant modes of inheritance have been described.[22] It is not known, however, how the genetic traits are expressed as myocardial dysfunction in cardiomyopathy. Although, in some cases, metabolic defects of the cardiac myocyte have been implicated, in others, an enhanced susceptibility to environmental agents or to immunological responses to them may be at fault. An immunological component was shown for the progression to chronic cardiac disease in experimental and human viral myocarditis.[23 24] It is widely assumed that many cases of dilated cardiomyopathy are the end result of a preceding viral infection the serological evidence for which has long since disappeared. It is suggested that the initial virus induced myocardial damage sets up an immunological reaction against intracellular constituents which further sustains and aggravates myocardial dysfunction. Immunological mechanisms would thus have a secondary role and contribute to a variable extent to the progression of the myopathic process. It is also possible, however, that genetically controlled immunological mechanisms participate more directly in the initiation of myocardial damage either through control of the susceptibility to the aetiological viral infection, or through modulation of the immunological response to the putative viral agents. There is precedent for both mechanisms: for example, it is known that histocompatibility antigens determine the cardiotoxicity of Coxsackie B viruses[24] or their interaction with specific tissues. Also, experimentally induced myocarditis induced in mice through induction of antimyosin antibodies is largely determined by the H-2 locus.[25]

This suggested that it would be useful to look for immunologically associated genetic markers of dilated cardiomyopathy in humans. The HLA antigens were selected because of their known participation in the regulation of immune responses and the previously reported association between specific haplotypes and autoimmune diseases. The results of our study suggest that the frequency of HLA-DR4 was significantly higher in patients with dilated cardiomyopathy than in controls. This accords with the results of a smaller series reported by Anderson *et al*.[26] On the other hand, the increase in HLA-B27 and the underrepresentation of HLA-DRw6 reported by Anderson *et al* were not confirmed in our series. In a series of patients with ischaemic cardiomyopathy, a preponderance of HLA-DRw6 antigen was found,[27] whereas in patients with alcoholic cardiomyopathy there was no association with any particular HLA haplotype. Also there is some evidence that HLA-DR3 is the antigen linked to hypertrophic cardiomyopathy.[28] This would indicate a certain degree of specificity in the association of different types of cardiomyopathy with immune genetic markers.

The calculated aetiological factor of 0·25 in our series probably underestimates the significance of the association with HLA-DR4 because of the heterogeneity of the pathological processes involved in dilated cardiomyopathy. For example, in a continuing study we found that the prevalence of autoantibodies against cardiac β adrenoceptors is almost 70% in HLA-DR4 positive patients with cardiomyopathy compared with only 25% in HLA-DR4 negative patients.[29] It is likely, therefore, that the increase in certain HLA antigens is linked to specific immunological disturbances, such as anti-receptor (or other autoantibody) production. Subsets of cardiomyopathy may then join the list of autoimmune diseases associated with anti-receptor antibodies. This has important implications for the classification and the pathophysiology of dilated cardiomyopathy as well as for new treatments. Support for such a pathogenetic role of class II HLA antigens may come from studies of their expression in the diseased myocardium. These antigens are not normally expressed in the heart[30] but may be abnormally expressed in pathological conditions such as rheumatic carditis[31] and cardiac transplant rejection.[30] It is not known whether myocardiopathic tissue expresses these antigens and it is important to find out if it does.

We found no correlation in this study between the presence of HLA-DR4 and the severity or duration of the disease. This may not be unexpected if the association is a marker for susceptibility to the disease but does not influence its progression or severity—a situation that is common to autoimmune diseases. On the other hand, if HLA-DR4 is a marker for a specific pathogenetic pathway (that is anti-receptor autoantibodies), there may be a correlation with disease severity within this subset of cardiomyopathy patients. The design of our study, which includes patients with severe haemodynamic impairment does not allow us unequivocally to exclude the possibility that HLA-DR4 positive patients have more severe disease or more rapid course. A prospective study of a population with a wider range of haemodynamic abnormalities is currently underway and should help resolve this issue.

References

1 Bolte HD, Schultheiss HP. Immunological results in myocardial disease. *Postgrad Med* 1978;54:500–3.

2 Teixeira ARL, Teixeira G, Macedo V, Prata A. *Trypanosoma cruzi* sensitized T-lymphocytes mediate ^{51}Cr release from human heart cells in Chagas' disease. *Am J Trop Med Hyg* 1978;27:1097–102.

3 Jacobs B, Matsuda Y, Deodhar S, Shirey E. Cell mediated cytotoxicity to cardiac cells of lymphocytes from patients with primary myocardial disease. *Am J Pathol* 1979;72:1–16.

4 Fowles RE, Bieber CP, Stinson EB. Defective *in vitro* suppressor cell in idiopathic congestive cardiomyopathy. *Circulation* 1974;59:483–91.

5 Anderson JL, Greenwood JH, Kawaniski H. Evaluation of suppressor immune regulatory function in idiopathic congestive cardiomyopathy and rheumatic heart disease. *Br Heart J* 1981;46:410–4.

6 Sack W, Sebening H, Wachsmut ED. Auto-antikorper gegen Herzmuskelsarkolemm im serum von patienten mit primarer kardiomyopathie. *Klin Wochenschr* 1975;35:103–10.

7 Oevermann W, Bolte HD, Zwehl W. Indirekter Immunofluoreszentest und indirekter antiglobulinkosumptions test in der diagnostik primarer kardiomyopathien. *Verh Dtsch Ges Inn Med* 1973;79:114–8.

8 Das SK, Collen JP, Dodson VN, Cassidy JT. Immunoglobulin binding in cardiomyopathic hearts. *Circulation* 1971;44:612–6.

9 Schultheiss HP, Bolte HD. Immunological analysis of autoantibodies against the adenine nucleotide translocator in dilated cardiomyopathy. *J Mol Cell Cardiol* 1985;12:603–17.

10 Bottazzo GF, Todd I, Mirakian R, Belfiore A, Pujol-Borrell R. Organ-specific autoimmunity: a 1986 overview. *Immunol Rev* 1986;94:137–59.

11 Feldmann N. Regulation of HLA class II expression and its role in autoimmune disease. *Ciba Found Symp* 1987;129:88–108.

12 Tiwari JL, Terasaki PI. *HLA and disease associations.* New York: Springer Verlag, 1985:542.

13 Bottazzo GF, Pujol-Borrell R, Hanafusa T, Feldmann M. Role of aberrant HLA-DR expression and antigen presentation in the induction of endocrine autoimmunity. *Lancet* 1983;ii:1115–9.

14 Boyum A. Isolation of lymphocytes, granulocytes and macrophages. *Scand J Immunol* 1976;5(suppl 5):9–15.

15 Danilovs JA, Ayoub G, Terasaki PI. B lymphocyte isolation by thrombin-nylon wool. In: Terasaki P, ed. *Histocompatibility testing.* Los Angeles: UCLA Tissue Typing Laboratory, 1980:287–8.

16 Terasaki PI, Clelland JD. Microdroplet assay of human serum cytotoxins. *Nature* 1964;204:998–1000.

17 Bodmer JE, Pickbourne P, Richards S. Serology. In: Bodmer WF, Batchelor JR, Bodmer JE, Festenstein H, Morris PH, eds. *Histocompatibility testing, 1977.* Copenhagen: Munksgaard, 1977:35–8.

18 Svejgaard A, Platz P, Ryder LP. HLA and disease 1982. *Immunol Rev* 1983;70:193–218.

19 Maisch B, Deeg P, Liebau G, Kochsiek K. Diagnostic relevance of humoral and cytotoxic immune reactions in primary and secondary dilated cardiomyopathy. *Am J Cardiol* 1983;52:1072–8.

20 Limas CJ, Goldenberg IF. Autoantibodies against cardiac β-adrenoceptors in human dilated cardiomyopathy. *Circ Res* 1989;64:97–103.

21 Taylor WJ. Genetic aspects of the cardiomyopathies. *Prog Med Genet* 1983;5:163–89.

22 Emanuel R, Withers R, O'Brien K. Dominant and recessive modes of inheritance in idiopathic cardiomyopathy. *Lancet* 1971;ii:1065–7.

23 Maisch B, Trostel-Soeder R, Stechemesser E, Berg PA, Kochsiek K. Diagnostic relevance of humoral and cell-mediated immune reactions in patients with acute viral myocarditis. *Clin Exp Immunol* 1986; **48**:553–45.

24 Wolfgram LJ, Beisel KW, Herskowitz A, Rose NR. Variations in the susceptibility to Coxsackievirus B_3-induced myocarditis among different strains of mice. *J Immunol* 1986;**136**:1846–52.

25 Neu N, Rose NR, Beisel KW, Herskowitz A, Gurri-Glass G, Craig SW. Cardiac myosin induces myocarditis in genetically predisposed mice. *J Immunol* 1987; **139**:3630–4.

26 Anderson JL, Carlquist JF, Lutz JR, DeWitt CW, Hammond EH. HLA A, B and DR typing in idiopathic dilated cardiomyopathy: a search for immune response factors. *Am J Cardiol* 1984; **53**:1326–30.

27 Limas CJ, Limas C. HLA-DRw6 antigen linkage in chronic congestive heart failure secondary to coronary artery disease (ischemic cardiomyopathy). *Am J Cardiol* 1988;**62**:816–8.

28 Fiorito S, Autore C, Fragola PV, Purpura M, Cannata D, Sangiorgi M. HLA-DR3 antigen linkage in patients with hypertrophic obstructive cardiomyopathy. *Am Heart J* 1986;**111**:91–4.

29 Limas CJ, Limas C, Kubo S. Anti-β-receptor antibodies in human dilated cardiomyopathy: relation to histo-compatibility antigens [Abstract]. *Circulation* 1988;**78**(suppl II):165.

30 Suitters A, Rose M, Higgins A, Yacoub MH. MHC antigen expression in sequential biopsies from cardiac transplant patients—correlation with rejection. *Clin Exp Immunol* 1987;**69**:575–83.

31 Amoils B, Morrison RC, Wadee AA, *et al.* Aberrant expression of HLA-DR antigen on valvular fibroblasts from patients with active rheumatic carditis. *Clin Exp Immunol* 1986;**66**:88–94.

Br Heart J 1989;**62**:384–8

Hypertrophic cardiomyopathy in identical twins

JOHN M REID,* ALAN B HOUSTON,† EILEEN LUNDMARK*

*From the *Department of Cardiology, Western Infirmary, and the †Department of Cardiology, Royal Hospital for Sick Children, Glasgow*

SUMMARY Hypertrophic cardiomyopathy was diagnosed in identical twin boys in early childhood. One underwent myomectomy at the age of 12 years because of progressive severe exertional dyspnoea accompanied by considerable obstruction of the left ventricular outflow tract shown on both echocardiography and cardiac catheterisation. Seven years later, at the age of 19, he remains incapacitated to a moderate degree. By contrast, the other twin has led a relatively normal life to date and no left ventricular outflow obstruction has been shown.

Since the recognition of hypertrophic cardiomyopathy in the 1950s,[1-5] there have been many studies of all aspects of the condition including clinical presentation, haemodynamic function, aetiology, and natural course. In more than half the patients a familial incidence was recognised, the trait being autosomal dominant. We report hypertrophic cardiomyopathy in identical twins with a striking difference in clinical severity.

Case reports

THE FIRST TWIN

The first twin was noted to have a cardiac murmur during routine school medical examination when he was five years old. He was symptom free and the clinical diagnosis was ventricular septal defect. He was first referred to the cardiac clinic when he was 11 because of increasing exertional dyspnoea accompanied by chest pain in the previous year.

On clinical examination there was no cardiomegaly but a loud ejection systolic murmur was audible over the entire precordium and maximal at the aortic area. There was evidence of left ventricular hypertrophy on the electrocardiogram and there was inversion of the T wave in the anteroseptal leads consistent with septal hypertrophy. Echocardiography showed asymmetrical septal hypertrophy with systolic anterior movement of the anterior cusp of the mitral valve. At cardiac catheterisation, there was no detectable intracardiac shunt but there was a systolic gradient of 80 mm Hg across the outflow tract of the left ventricle. The diagnosis of hypertrophic cardiomyopathy was established and treatment with propranolol was started. Because his breathlessness became worse a repeat investigation was carried out next year and the gradient had increased to 120 mm Hg. Operation was recommended and subaortic myomectomy was carried out. At operation, the aortic valve was normal but there was a tight subaortic stenosis extending 2·5 cm below the valve. On inspection the anterior leaflet of the mitral valve was normal. Myomectomy was carried out to a depth of 7 mm and a width of 10 mm to enlarge the outflow diameter to 22 mm. The gradient was reduced to 15 mm Hg. He was examined each year and he remained considerably incapacitated with persistent left ventricular hypertrophy on the electrocardiogram. Cross sectional echocardiography in 1988 once again showed considerable septal hypertrophy (fig 1).

The short axis sweep from apex to aortic root showed disproportionate thickening of the septum compared with the posterior wall. The gradient both at Doppler examination and repeat catheterisation was 35 mm Hg. Further operation was deferred but treatment with propranolol was changed to verapamil.

THE SECOND TWIN

The second twin was referred to us at the age of 11 years because of an indeterminate episode of chest pain and mild exertional dyspnoea over the preceding year. Clinical examination showed no cardiomegaly and no cardiac murmurs were audible. Chest *x* ray showed no cardiac enlargement and there was no evidence of ventricular hypertrophy on the electrocardiogram; a Q wave was present, however, in limb lead II and in V6. Echocardiography showed concentric thickening of the left ventricle but the aortic and mitral valves appeared normal. Forty eight

Requests for reprints to Dr John M Reid, Department of Cardiology, Western Infirmary, Dumbarton Road, Glasgow G11 6NT.

Accepted for publication 3 July 1989

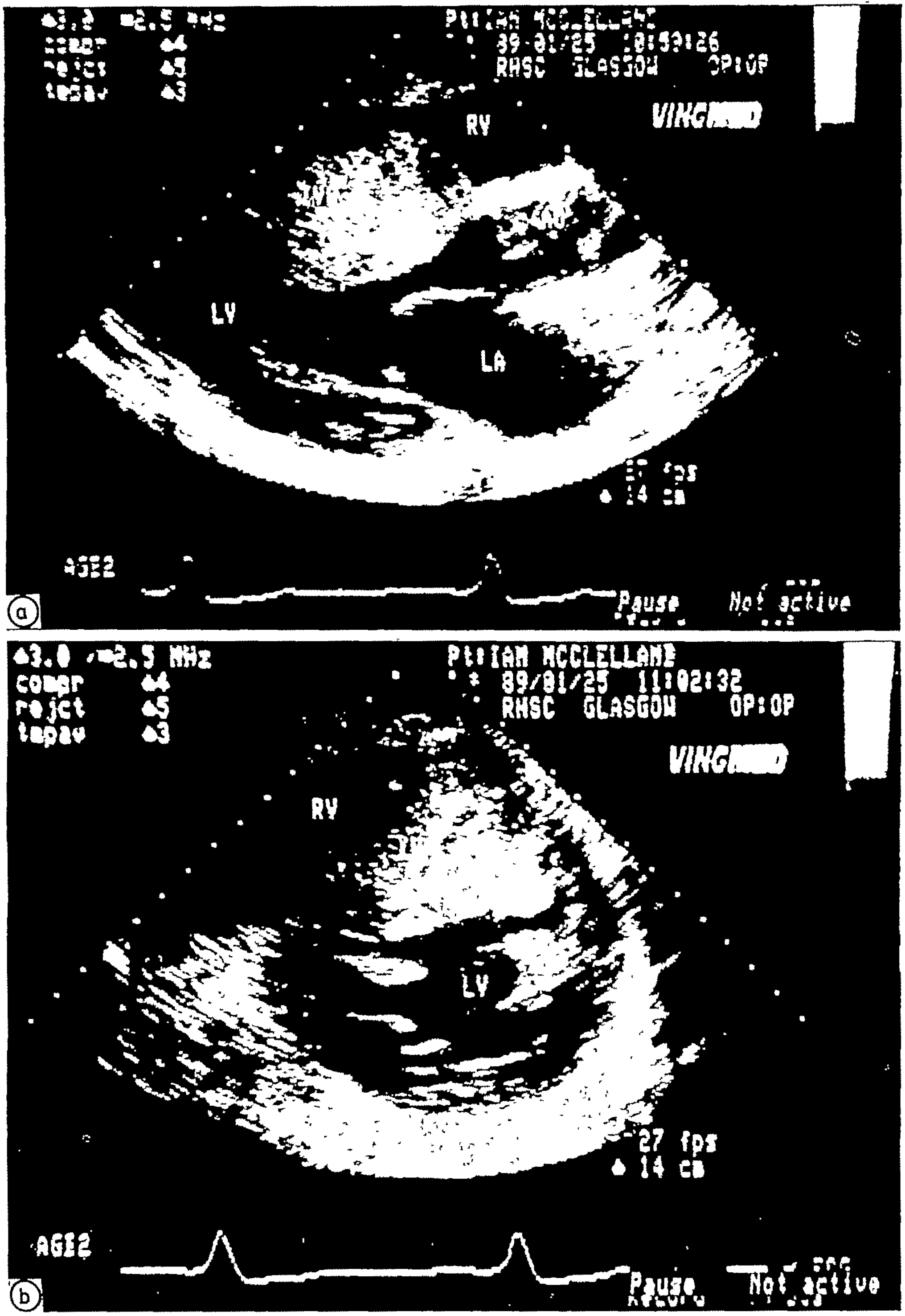


Fig 1 *Cross sectional echocardiographic views in diastole from patient 1. (a) Long axis and (b) short axis at tips of mitral valves. RV, right ventricle; IVS, ventricular septum; LV, left ventricle; LA, left atrium; AO, aorta.*

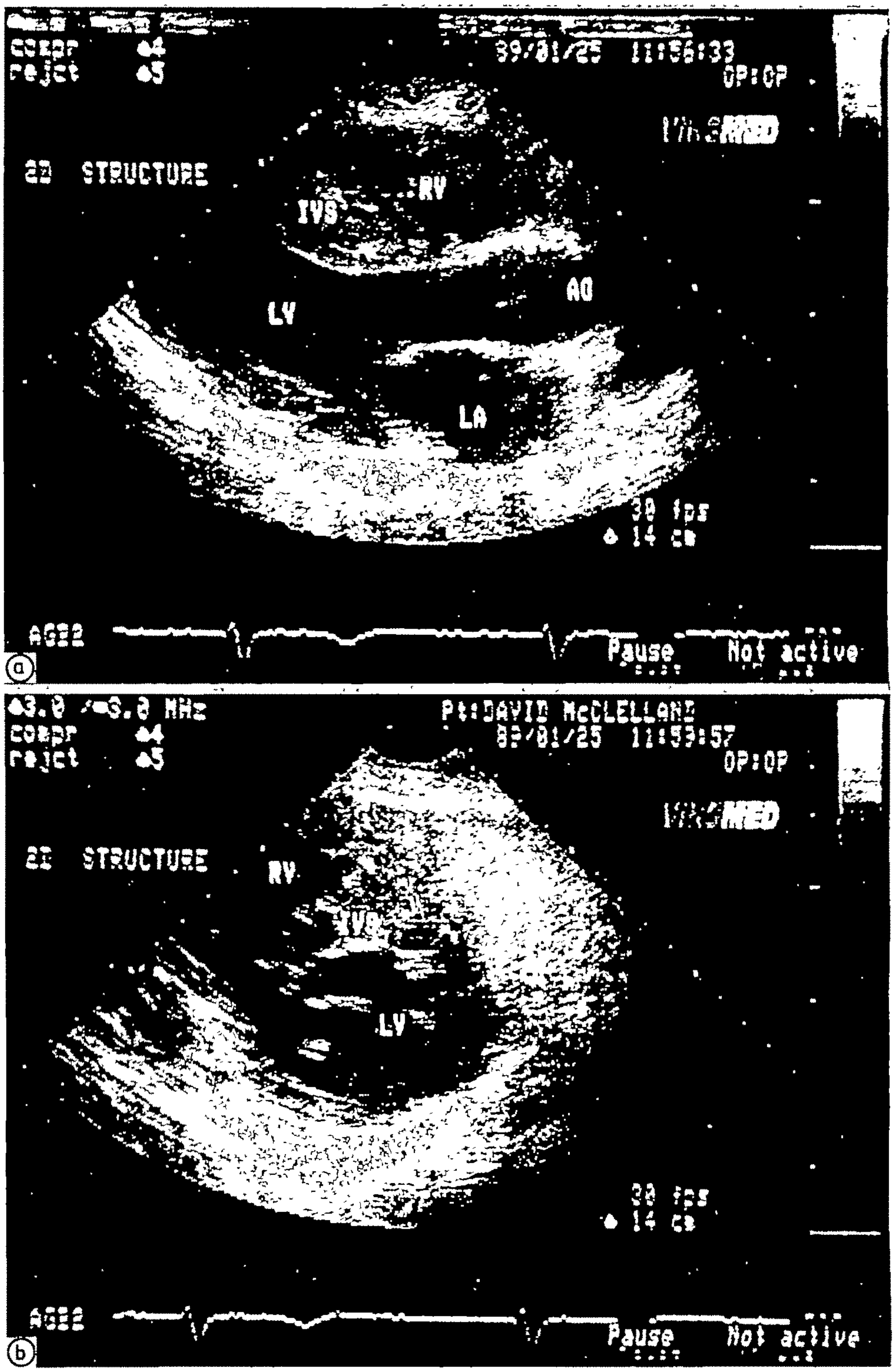


Fig 2 *Cross sectional echocardiographic views in diastole from patient 2. (a) Long axis and (b) short axis. See legend to fig 1 for abbreviations.*

hour Holter monitoring showed infrequent short bursts of paroxysmal supraventricular tachycardia. A diagnosis of hypertrophic cardiomyopathy was not conclusive at this time but verapamil was introduced to control the short bursts of supraventricular tachycardia. Cardiac catheterisation and angiocardiography were carried out in 1985 when the patient was 15 years old and this showed normal left ventricular function, no aortic regurgitation, and no gradient across the left ventricular outflow tract. The most recent echocardiographic assessment carried out in 1988 showed thickening of both the interventricular septum and the posterior wall of the left ventricle but with only slight systolic anterior movement of the mitral valve (fig 2).

The diagnosis of hypertrophic cardiomyopathy was established but the patient remains well and at work.

Testing with Jeffries's hypervariable DNA probe confirmed that the DNA fingerprints were identical and that the twins were monozygotic. The mother of the twins was examined and although clinical examination was unremarkable, echocardiographic and Doppler studies showed thickening of the interventricular septum, but there was neither systolic anterior movement of the mitral valve nor left ventricular outflow obstruction.

Discussion

Hypertrophic cardiomyopathy is known to be a familial condition. Greaves *et al* studied 193 first degree relatives of 50 patients with the condition by clinical examination, electrocardiography, and cross sectional echocardiography.[6] In 28 of the 50 families studied a familial occurrence was recorded; in 15 the pattern was consistent with an autosomal dominant trait. Maron and Mulvihill in a review of the genetics of hypertrophic cardiomyopathy concluded that between 50 and 90% of reported cases were familial,[7] and the condition was recorded in three generations of a large Norwegian family.[8] There is, however, no mention in published reports of the occurrence of hypertrophic cardiomyopathy in twins.

Both our patients were monozygotic twins (confirmed on testing with the Jeffries's hypervariable DNA probe) and presented in childhood. In the first, the condition was rapidly progressive and the boy required myomectomy at an early age. The other twin by comparison has lived a normal life throughout 10 years' supervision. The morphology of hypertrophic cardiomyopathy can be heterogeneous[9] and the patterns and extent of left ventricular hypertrophy can vary greatly.[10] These features can influence the course and clinical features of the condition as they did in our twins. Although both the diastolic and systolic function of the left ventricle are impaired in hypertrophic cardiomyopathy, the disordered haemodynamic function affecting both diastolic filling and distensibility of the left ventricle seems to be the principal factor leading to progression of the disease and the onset of symptoms such as exertional dyspnoea, angina, variable types of arrhythmias and, in severe cases, transient syncopal episodes.[10] The most serious arrhythmias reported are supraventricular and ventricular tachycardia, aberrant atrioventricular nodal pathways, and complete heart block. The disturbance most predictive of sudden death is ventricular tachycardia. The annual mortality is 2–3%,[11 12] tending to affect predominantly younger patients, particularly when there is a family history of the condition. In the first twin left ventricular hypertrophy with strain was present on the electrocardiogram but 24 hour ambulatory electrocardiographic monitoring showed no serious arrhythmias and only infrequent ventricular extrasystoles despite the severity of his condition. His twin brother, however, had several episodes of supraventricular tachycardia on Holter monitoring. The difference in clinical presentation in these twins is most striking and unusual.

Serial echocardiographic and Doppler studies are most important in the long term management of these patients. The sheet-anchor in the management is medication with either β blockers, calcium channel blockers, or in some cases both.[13 14] Verapamil improved left ventricular diastolic function by improving rapid diastolic filling—thereby increasing exercise tolerance and leading to symptomatic improvement.[15] Amiodarone has also been shown to be effective[16] but side effects tend to become increasingly common the longer the duration of treatment.[17] The role of cardiac surgery in hypertrophic cardiomyopathy is still somewhat controversial.[18 19] Surgical treatment is undoubtedly indicated when the outflow gradient exceeds 50 mm Hg, and there is substantial evidence that operation can improve symptoms and the quality of life. There is no conclusive evidence to date, however, that it does in fact prolong life. Subaortic myomectomy in our first twin undoubtedly produced considerable clinical benefit with lessening of the left ventricular outflow gradient. To date, surgical treatment has not been necessary in his twin brother. A more recent innovation is that of transarterial laser myoplasty,[20] but again its precise role in the overall management of the condition has yet to be defined. Its principal advantage seems to be that the procedure can be repeated if necessary.

We thank Mr J C S Pollock, FRCS, who carried out the surgical treatment in patient 1.

References

1 Brock R. Functional obstruction of the left ventricle (acquired aortic subvalvar stenosis). *Guy's Hospital Rep* 1957;**106**:221–38.

2 Teare D. Asymmetrical hypertrophy of the heart in young adults. *Br Heart J* 1958;**20**:1–8.

3 Bercu BA, Diettert GA, Danforth WH, Pand EE Jr, Ahlvin RC, Belliveau RR. Pseudoaortic stenosis produced by ventricular hypertrophy. *Am J Med* 1958;**25**:814–8.

4 Goodwin JF, Hollman A, Cleland WP, Teare D. Obstructive cardiomyopathy simulating aortic stenosis. *Br Heart J* 1960;**22**:403–14.

5 Morrow AG, Braunwald E. Functional aortic stenosis; a malformation characterised by resistance to left ventricular outflow without anatomic obstruction. *Circulation* 1959;**20**:181–9.

6 Greaves SC, Roche AHG, Neutze JM, Whitlock RML, Veale AMO. Inheritance of hypertrophic cardiomyopathy: a cross sectional and M mode echocardiographic study of 50 families. *Br Heart J* 1987;**58**:259–66.

7 Maron BJ, Mulvihill JJ. The genetics of hypertrophic cardiomyopathy. *Ann Intern Med* 1986;**105**:610–2.

8 Haughland H, Ohm O-J, Boman H, Thorsby E. Hypertrophic cardiomyopathy in three generations of a large Norwegian family: a clinical, echocardiographic, and genetic study. *Br Heart J* 1986;**55**:168–75.

9 Ciro E, Nichol PF, Maron BJ. Heterogenous morphologic expression of genetically transmitted hypertrophic cardiomyopathy. Two dimensional echocardiographic analysis. *Circulation* 1983;**67**: 1227–33.

10 Maron BJ, Bonow RO, Cannon RO, Leon MB, Epstein SE. Medical progress. Hypertrophic cardiomyopathy. Interrelations of clinical manifestations, pathophysiology, and therapy. *N Engl J Med* 1987;**316**:780–9.

11 Shah PM, Adelman AG, Wigle ED, *et al.* The natural (and unnatural) history of hypertrophic obstructive cardiomyopathy. *Circ Res* 1973;**34** and **35**(suppl 2):II 179–95.

12 Maron BJ, Savage DD, Wolfson JK, Epstein SE. Prognostic significance of 24 hour ambulatory electrocardiographic monitoring in patients with hypertrophic cardiomyopathy: a prospective study. *Am J Cardiol* 1981;**48**:252–7.

13 Harrison DC, Braunwald E, Glick G, Mason DT, Chidsey CA, Ross J Jr. Effects of beta adrenergic blockade on the circulation, with particular reference to observations in patients with hypertrophic subaortic stenosis. *Circulation* 1964;**29**:84–98.

14 Brigden W. Hypertrophic cardiomyopathy. *Br Heart J* 1987;**58**:299–302.

15 Bonow RU, Dulsizian V, Rosing DR, Maron BJ, Bacharach SL, Green MV. Verapamil induced improvement in left ventricular diastolic filling and increased exercise tolerance in patients with hypertrophic cardiomyopathy: short and long term effects. *Circulation* 1985;**72**:853–64.

16 McKenna WJ, Harris L, Rowland E, *et al.* Amiodarone for long term management of patients with hypertrophic cardiomyopathy. *Am J Cardiol* 1984;**54**: 802–10.

17 Paulus WJ, Nellens P, Heyndrickx GR, Andries E. Effects of long term treatment with amiodarone on exercise haemodynamics and left ventricular relaxation in patients with hypertrophic cardiomyopathy. *Circulation* 1986;**74**:544–54.

18 Morrow AG, Reitz BA, Epstein SE, *et al.* Operative treatment in hypertrophic subaortic stenosis; techniques, and the results of pre and post operative assessments in 83 patients. *Circulation* 1975;**52**: 82–102.

19 Bircks W, Schulte HD. Surgical treatment of hypertrophic obstructive cardiomyopathy with special reference to complications and to atypical hypertrophic obstructive cardiomyopathy. *Eur Heart J* 1983;4 (suppl F):187–90.

20 Serruys PW, den Boer A. What will be the requirement for acute interventional procedures in Europe? *Eur Heart J* 1987;**8** (suppl F):55–9.

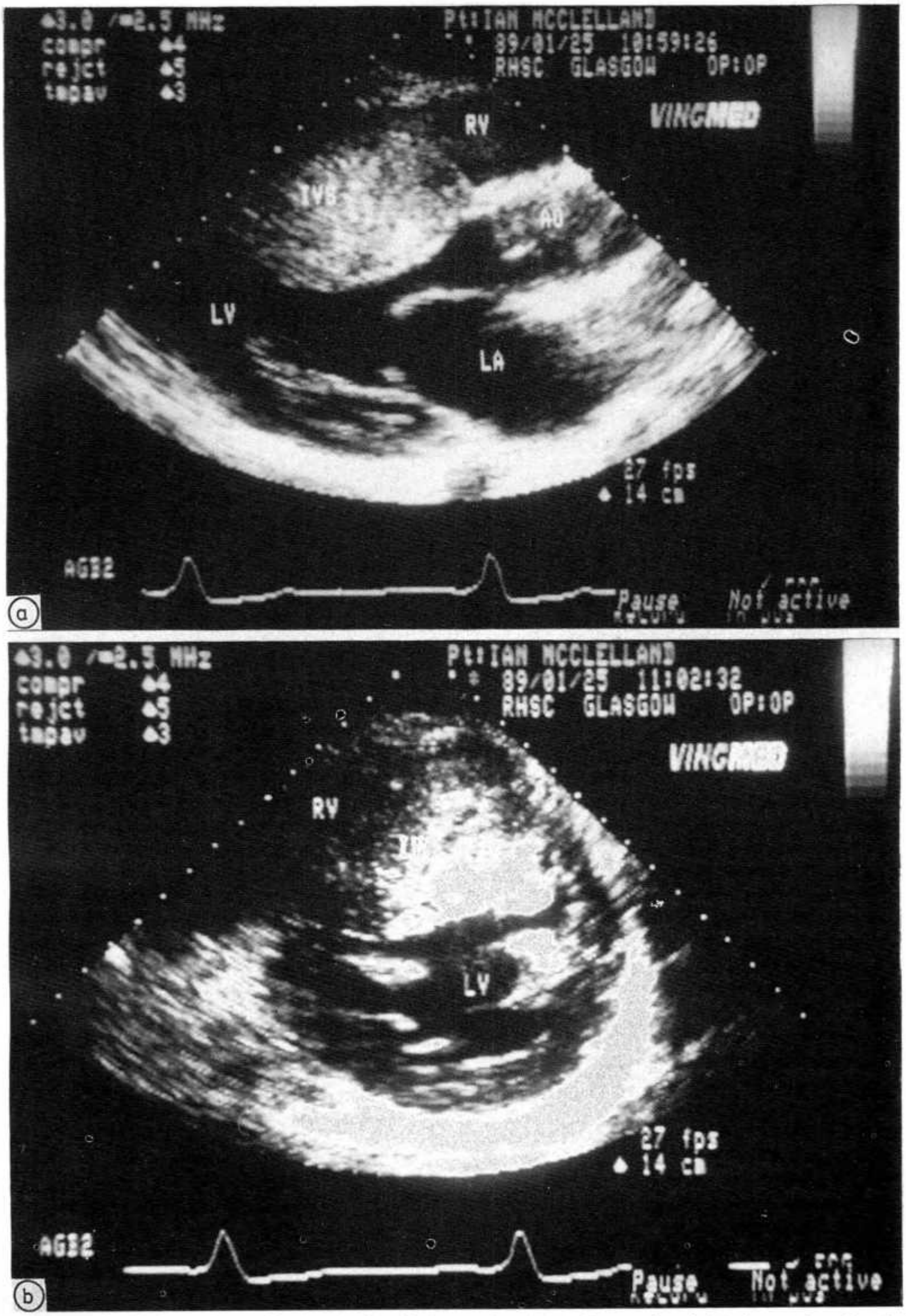


Fig 1 *Cross sectional echocardiographic views in diastole from patient 1. (a) Long axis and (b) short axis at tips of mitral valves. RV, right ventricle; IVS, ventricular septum; LV, left ventricle; LA, left atrium; AO, aorta.*

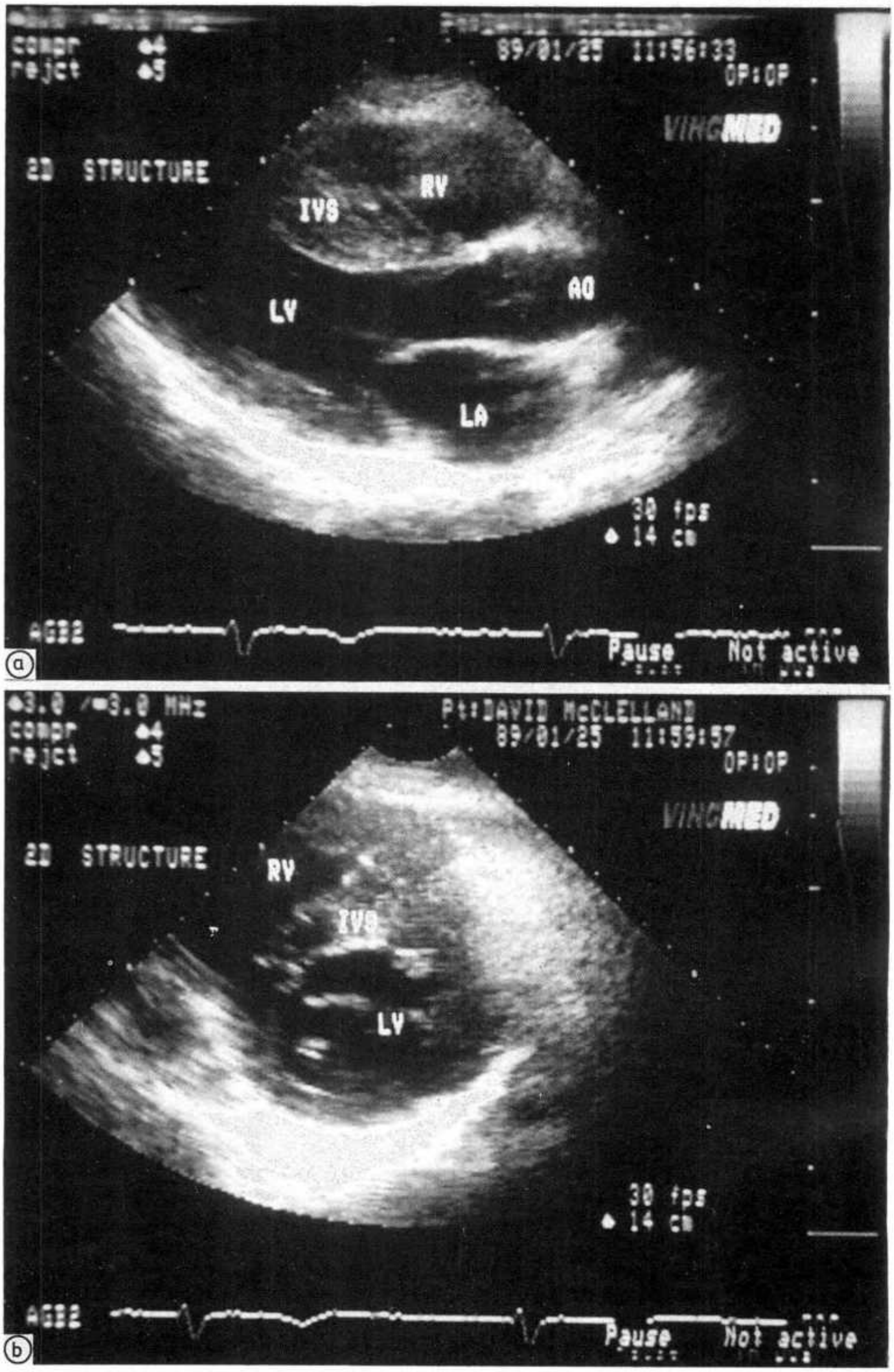


Fig 2 *Cross sectional echocardiographic views in diastole from patient 2. (a) Long axis and (b) short axis. See legend to fig 1 for abbreviations.*

hour Holter monitoring showed infrequent short bursts of paroxysmal supraventricular tachycardia. A diagnosis of hypertrophic cardiomyopathy was not conclusive at this time but verapamil was introduced to control the short bursts of supraventricular tachycardia. Cardiac catheterisation and angiocardiography were carried out in 1985 when the patient was 15 years old and this showed normal left ventricular function, no aortic regurgitation, and no gradient across the left ventricular outflow tract. The most recent echocardiographic assessment carried out in 1988 showed thickening of both the interventricular septum and the posterior wall of the left ventricle but with only slight systolic anterior movement of the mitral valve (fig 2).

The diagnosis of hypertrophic cardiomyopathy was established but the patient remains well and at work.

Testing with Jeffries's hypervariable DNA probe confirmed that the DNA fingerprints were identical and that the twins were monozygotic. The mother of the twins was examined and although clinical examination was unremarkable, echocardiographic and Doppler studies showed thickening of the interventricular septum, but there was neither systolic anterior movement of the mitral valve nor left ventricular outflow obstruction.

Discussion

Hypertrophic cardiomyopathy is known to be a familial condition. Greaves *et al* studied 193 first degree relatives of 50 patients with the condition by clinical examination, electrocardiography, and cross sectional echocardiography.[6] In 28 of the 50 families studied a familial occurrence was recorded; in 15 the pattern was consistent with an autosomal dominant trait. Maron and Mulvihill in a review of the genetics of hypertrophic cardiomyopathy concluded that between 50 and 90% of reported cases were familial,[7] and the condition was recorded in three generations of a large Norwegian family.[8] There is, however, no mention in published reports of the occurrence of hypertrophic cardiomyopathy in twins.

Both our patients were monozygotic twins (confirmed on testing with the Jeffries's hypervariable DNA probe) and presented in childhood. In the first, the condition was rapidly progressive and the boy required myomectomy at an early age. The other twin by comparison has lived a normal life throughout 10 years' supervision. The morphology of hypertrophic cardiomyopathy can be heterogeneous[9] and the patterns and extent of left ventricular hypertrophy can vary greatly.[10] These features can influence the course and clinical features of the condition as they did in our twins. Although both the diastolic and systolic function of the left ventricle are impaired in hypertrophic cardiomyopathy, the disordered haemodynamic function affecting both diastolic filling and distensibility of the left ventricle seems to be the principal factor leading to progression of the disease and the onset of symptoms such as exertional dyspnoea, angina, variable types of arrhythmias and, in severe cases, transient syncopal episodes.[10] The most serious arrhythmias reported are supraventricular and ventricular tachycardia, aberrant atrioventricular nodal pathways, and complete heart block. The disturbance most predictive of sudden death is ventricular tachycardia. The annual mortality is 2–3%,[11 12] tending to affect predominantly younger patients, particularly when there is a family history of the condition. In the first twin left ventricular hypertrophy with strain was present on the electrocardiogram but 24 hour ambulatory electrocardiographic monitoring showed no serious arrhythmias and only infrequent ventricular extrasystoles despite the severity of his condition. His twin brother, however, had several episodes of supraventricular tachycardia on Holter monitoring. The difference in clinical presentation in these twins is most striking and unusual.

Serial echocardiographic and Doppler studies are most important in the long term management of these patients. The sheet-anchor in the management is medication with either β blockers, calcium channel blockers, or in some cases both.[13 14] Verapamil improved left ventricular diastolic function by improving rapid diastolic filling—thereby increasing exercise tolerance and leading to symptomatic improvement.[15] Amiodarone has also been shown to be effective[16] but side effects tend to become increasingly common the longer the duration of treatment.[17] The role of cardiac surgery in hypertrophic cardiomyopathy is still somewhat controversial.[18 19] Surgical treatment is undoubtedly indicated when the outflow gradient exceeds 50 mm Hg, and there is substantial evidence that operation can improve symptoms and the quality of life. There is no conclusive evidence to date, however, that it does in fact prolong life. Subaortic myomectomy in our first twin undoubtedly produced considerable clinical benefit with lessening of the left ventricular outflow gradient. To date, surgical treatment has not been necessary in his twin brother. A more recent innovation is that of transarterial laser myoplasty,[20] but again its precise role in the overall management of the condition has yet to be defined. Its principal advantage seems to be that the procedure can be repeated if necessary.

We thank Mr J C S Pollock, FRCS, who carried out the surgical treatment in patient 1.

References

1 Brock R. Functional obstruction of the left ventricle (acquired aortic subvalvar stenosis). *Guy's Hospital Rep* 1957;**106**:221–38.

2 Teare D. Asymmetrical hypertrophy of the heart in young adults. *Br Heart J* 1958;**20**:1–8.

3 Bercu BA, Diettert GA, Danforth WH, Pand EE Jr, Ahlvin RC, Belliveau RR. Pseudoaortic stenosis produced by ventricular hypertrophy. *Am J Med* 1958;**25**:814–8.

4 Goodwin JF, Hollman A, Cleland WP, Teare D. Obstructive cardiomyopathy simulating aortic stenosis. *Br Heart J* 1960;**22**:403–14.

5 Morrow AG, Braunwald E. Functional aortic stenosis; a malformation characterised by resistance to left ventricular outflow without anatomic obstruction. *Circulation* 1959;**20**:181–9.

6 Greaves SC, Roche AHG, Neutze JM, Whitlock RML, Veale AMO. Inheritance of hypertrophic cardiomyopathy: a cross sectional and M mode echocardiographic study of 50 families. *Br Heart J* 1987;**58**:259–66.

7 Maron BJ, Mulvihill JJ. The genetics of hypertrophic cardiomyopathy. *Ann Intern Med* 1986;**105**:610–2.

8 Haughland H, Ohm O-J, Boman H, Thorsby E. Hypertrophic cardiomyopathy in three generations of a large Norwegian family: a clinical, echocardiographic, and genetic study. *Br Heart J* 1986;**55**:168–75.

9 Ciro E, Nichol PF, Maron BJ. Heterogenous morphologic expression of genetically transmitted hypertrophic cardiomyopathy. Two dimensional echocardiographic analysis. *Circulation* 1983;**67**:1227–33.

10 Maron BJ, Bonow RO, Cannon RO, Leon MB, Epstein SE. Medical progress. Hypertrophic cardiomyopathy. Interrelations of clinical manifestations, pathophysiology, and therapy. *N Engl J Med* 1987;**316**:780–9.

11 Shah PM, Adelman AG, Wigle ED, *et al.* The natural (and unnatural) history of hypertrophic obstructive cardiomyopathy. *Circ Res* 1973;**34** and **35**(suppl 2):II 179–95.

12 Maron BJ, Savage DD, Wolfson JK, Epstein SE. Prognostic significance of 24 hour ambulatory electrocardiographic monitoring in patients with hypertrophic cardiomyopathy: a prospective study. *Am J Cardiol* 1981;**48**:252–7.

13 Harrison DC, Braunwald E, Glick G, Mason DT, Chidsey CA, Ross J Jr. Effects of beta adrenergic blockade on the circulation, with particular reference to observations in patients with hypertrophic subaortic stenosis. *Circulation* 1964;**29**:84–98.

14 Brigden W. Hypertrophic cardiomyopathy. *Br Heart J* 1987;**58**:299–302.

15 Bonow RU, Dulsizian V, Rosing DR, Maron BJ, Bacharach SL, Green MV. Verapamil induced improvement in left ventricular diastolic filling and increased exercise tolerance in patients with hypertrophic cardiomyopathy: short and long term effects. *Circulation* 1985;**72**:853–64.

16 McKenna WJ, Harris L, Rowland E, *et al.* Amiodarone for long term management of patients with hypertrophic cardiomyopathy. *Am J Cardiol* 1984;**54**:802–10.

17 Paulus WJ, Nellens P, Heyndrickx GR, Andries E. Effects of long term treatment with amiodarone on exercise haemodynamics and left ventricular relaxation in patients with hypertrophic cardiomyopathy. *Circulation* 1986;**74**:544–54.

18 Morrow AG, Reitz BA, Epstein SE, *et al.* Operative treatment in hypertrophic subaortic stenosis; techniques, and the results of pre and post operative assessments in 83 patients. *Circulation* 1975;**52**:82–102.

19 Bircks W, Schulte HD. Surgical treatment of hypertrophic obstructive cardiomyopathy with special reference to complications and to atypical hypertrophic obstructive cardiomyopathy. *Eur Heart J* 1983;4 (suppl F):187–90.

20 Serruys PW, den Boer A. What will be the requirement for acute interventional procedures in Europe? *Eur Heart J* 1987;**8** (suppl F):55–9.

Br Heart J 1989;62:389–95

Anomalous origin of one pulmonary artery from the ascending aorta: a review of echocardiographic, catheter, and morphological features

LANCE V FONG,* ROBERT H ANDERSON,† RALPH D SIEWERS,‡
ALFREDO TRENTO,‡ SANG C PARK‡

*From the *Wessex Cardiothoracic Centre, Southampton General Hospital, Southampton; †National Heart and Lung Institute, London; and ‡Departments of Paediatrics and Surgery, University of Pittsburgh School of Medicine, Children's Hospital of Pittsburgh, Pittsburgh, USA*

SUMMARY Six patients with anomalous origin of one pulmonary artery from the ascending aorta were reviewed. Four had anomalous origin of the right pulmonary artery and two had anomalous origin of the left pulmonary artery from the ascending aorta. Two of these six patients had tetralogy of Fallot. Two patients died in the first month of life. No changes in the pulmonary vasculature were seen at necropsy. Corrective surgery was attempted in two patients with associated tetralogy of Fallot when they were two years old but both died. At necropsy there was severe pulmonary vascular disease in the lung supplied by the anomalous pulmonary artery but no pulmonary vascular hypertensive changes in the lung supplied by the pulmonary artery from the right ventricle. Two recent patients underwent successful anastomosis of the anomalous pulmonary artery to the main pulmonary artery at three months and one month and three weeks of age respectively. Intraoperative lung biopsy in the latter patient showed early changes in both lungs. Both echocardiography and cardiac catheterisation were used in the diagnoses. Systemic or suprasystemic pressures were found in the pulmonary artery arising from the right ventricle as well as the anomalous pulmonary artery in the three patients without tetralogy of Fallot.

Anomalous origin of a pulmonary artery from the ascending aorta is a distinct entity and differs from other aorto-pulmonary arterial connections. Early surgical intervention is recommended in all patients (including those patients with associated tetralogy of Fallot) because of the risk of rapid development of irreversible pulmonary vascular disease.

Anomalous origin of one pulmonary artery from the ascending aorta with the contralateral pulmonary artery arising from the right ventricle is a rare congenital cardiac abnormality. The lesion must be distinguished from other arrangements in which the origin of one pulmonary artery is atretic but the arterial supply is derived either from a ductus arteriosus (arterial duct) or via collaterals between the systemic and pulmonary arteries.[1 2]

We reviewed the detailed findings, including diagnostic data and surgical considerations, in six patients with direct origin of one pulmonary artery from the ascending aorta. The morphology seen in four hearts at necropsy and the histopathology of the pulmonary vasculature at necropsy or lung biopsy were also examined.

Patients and methods

STUDY PATIENTS

From January 1968 to July 1987, six patients (two male, four female) with anomalous origin of one pulmonary artery from the ascending aorta were seen at the Children's Hospital of Pittsburgh. Four patients presenting in the first two months of life with congestive cardiac failure had the right (three) or left (one) pulmonary artery arising from the ascending aorta. Diagnosis was made at necropsy in the earliest case and by echocardiography or cardiac catheterisa-

Requests for reprints to Dr Lance V Fong, Wessex Cardiothoracic Centre, Southampton General Hospital, Southampton SO9 4XY.

Accepted for publication 4 July 1989

tion in the others. Two patients presented with cyanosis and a murmur when they were six months old. They had tetralogy of Fallot with a right aortic arch and a right (one) or left (one) pulmonary artery arising from the ascending aorta. In all patients the other pulmonary artery arose from the right ventricle.

One patient (case 1) (table) had Down's syndrome with duodenal atresia and prematurity while another (case 2) had clinical findings of the Di George syndrome with absence of the thymus at necropsy. The other patients had no extracardiac abnormalities.

DIAGNOSTIC STUDIES

Echocardiography was performed in the two most recent patients before cardiac catheterisation and again in the postoperative period. Five patients underwent cardiac catheterisation. Diagnosis was made at necropsy in the first patient of the series. In all patients we measured the size of the pulmonary arteries at the hilum, the distance of the anomalous origin above the aortic valve, and the length of the anomalous pulmonary artery from its origin with the aorta to its branching point. These measurements were taken from angiograms except in the patient not undergoing cardiac catheterisation. In this patient measurements were taken from the necropsy specimen.

COURSE

Operation was not performed on the earliest two patients in the series (cases 1 and 2) (table) although diagnosis had been confirmed by cardiac catheterisation in the second patient. Both died in the first month. Two other patients (cases 3 and 4) with tetralogy of Fallot underwent attempted surgical correction at 25 and 26 months of age but both died in the early postoperative period. Necropsy specimens of the heart and lung were available from these four patients. The last two patients in the series, who were diagnosed by echocardiography and angiography, underwent successful operative repair at three months and one month and three weeks of age. Open biopsies were performed on both lungs at the time of surgical repair in one patient (case 6).

Results

ECHOCARDIOGRAPHY

The parasternal long axis view (fig 1a) showed the anomalous posterolateral origin of the pulmonary artery from the ascending aorta a short distance above the aortic valve. The ascending aorta and the anomalous pulmonary artery were more extensively visualised with the transducer in a more cephalad position than that providing the usual long axis parasternal view. The ascending vessel above the pulmonary artery was shown to continue as the aortic arch, confirming that the vessel was the aorta and not the pulmonary artery. The size of the anomalous pulmonary artery was normal. Its course could be followed from suprasternal views by directing the transducer towards the right or left lung. The expected bifurcation of the pulmonary trunk could not be seen from either the parasternal or suprasternal short axis views (fig 1b). However, one patient had a large left atrial appendage which simulated a

Table *Data on six patients with anomalous origin of one pulmonary artery from the ascending aorta*

		Haemodynamic function (mm Hg)			*Surgery (mnth)*		*Lung histopathology*		
Patient	*Diagnosis*	*RPA*	*LPA*	*AO*	*Age*	*Type*	*Right*	*Left*	*Outcome*
1	RPA-AO DA LAA	—	—	—	—	—	Normal	Normal	Dead (3 wk)
2	RPA-AO DA LAA	90/50	105/55	90/50	—	—	Normal	Normal	Dead (2 wk)
3	LPA-AO TOF RAA	12/4	—	110/60	26	TOF repair, LPA anastomosis	Normal	Severe vascular changes	Dead (26 mnth)
4	RPA-AO TOF ALSA RAA	65/40	—	100/40	25	Conduit to RPA	Severe vascular changes	Normal	Dead (25 mnth)
5	LPA-AO DA ALSA RAA	90/40	—	95/40	3	LPA anastomosis, DA ligation	—	—	Alive
6	RPA-AO DA LAA	—	95/40	75/-	1 8	RPA anastomosis, DA ligation	Early vascular changes	Early vascular changes	Alive

ALSA, anomalous left subclavian artery; DA, ductus arteriosus; LAA, left aortic arch; LPA, left pulmonary artery; AO, ascending aorta; RAA, right aortic arch; RPA, right pulmonary artery; TOF, tetralogy of Fallot.

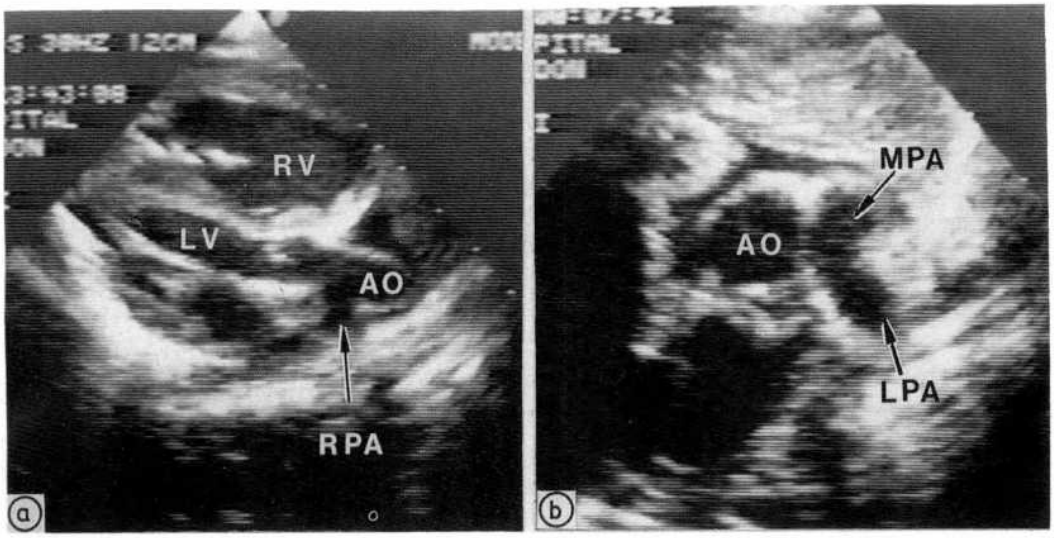


Fig 1 *Echocardiograms. (a) Parasternal long axis view of the right pulmonary artery (RPA) arising posteriorly from t ascending aorta (AO) (patient 6). (b) Suprasternal view of the left pulmonary artery (LPA) arising from the main pulmonary artery (MPA) (patient 6). LV, left ventricle; RV, right ventricle.*

right pulmonary artery in parasternal views. The postoperative connection of the anomalous pulmonary artery to the pulmonary trunk was visualised in parasternal short axis views. It arose from a proximal surgically favourable position.

HAEMODYNAMIC FUNCTION

A low pressure in the pulmonary artery connected to the right ventricle was confirmed in patient 3 with tetralogy of Fallot (table). The left pulmonary artery arising from the right ventricle in the other patient (case 4) with tetralogy was not entered but the right ventricular outflow tract was considerably obstructed. An unexplained moderate pressure difference was found between the anomalous right pulmonary artery and aorta in the absence of stenosis at the origin of the anomalous pulmonary artery.

Pressures in the normally connected pulmonary artery were systemic or suprasystemic in all three patients (2, 5, and 6) in whom there was no right ventricular outflow obstruction. The anomalous pulmonary artery was not entered in two of these three patients, but the pressure in the artery was likely to be similar to that in the ascending aorta.

OPERATION

Both patients with tetralogy of Fallot underwent attempted surgical repair at 25 and 26 months of age. Under cardiopulmonary bypass and through a right ventriculotomy, repair in the first patient included resection of the subpulmonary infundibulum, closure of the ventricular septal defect, positioning a pericardial transannular patch, and detachment of the anomalous left pulmonary artery from the ascending aorta with direct anastomosis to the pulmonary trunk. In the other patient, who had a severely hypoplastic right ventricular outflow tract, a conduit was placed between the right ventricle and the detached anomalous right pulmonary artery, the ventricular septal defect was closed, and the subpulmonary infundibulum was resected. The hypoplastic left pulmonary artery was not incorporated into the conduit. The aortic defect was sutured directly. Both patients died soon after operation. Pressures in the right ventricle were persistently high and cardiac output poor.

The last two patients underwent successful operative detachment of the anomalous pulmonary artery from the ascending aorta with subsequent direct anastomosis to the pulmonary trunk. Operation was completed without cardiopulmonary bypass in one patient when the left pulmonary artery arose from the aorta. Both patients had an uneventful postoperative course.

MORPHOLOGY

The anomalous pulmonary artery originated from the posterolateral aspect of the ascending aorta between 5 and 20 mm from the aortic valve (fig 2a and b). In two patients the anomalous right pulmonary artery arose from the posterior left aspect of the ascending aorta and then passed behind the aorta to

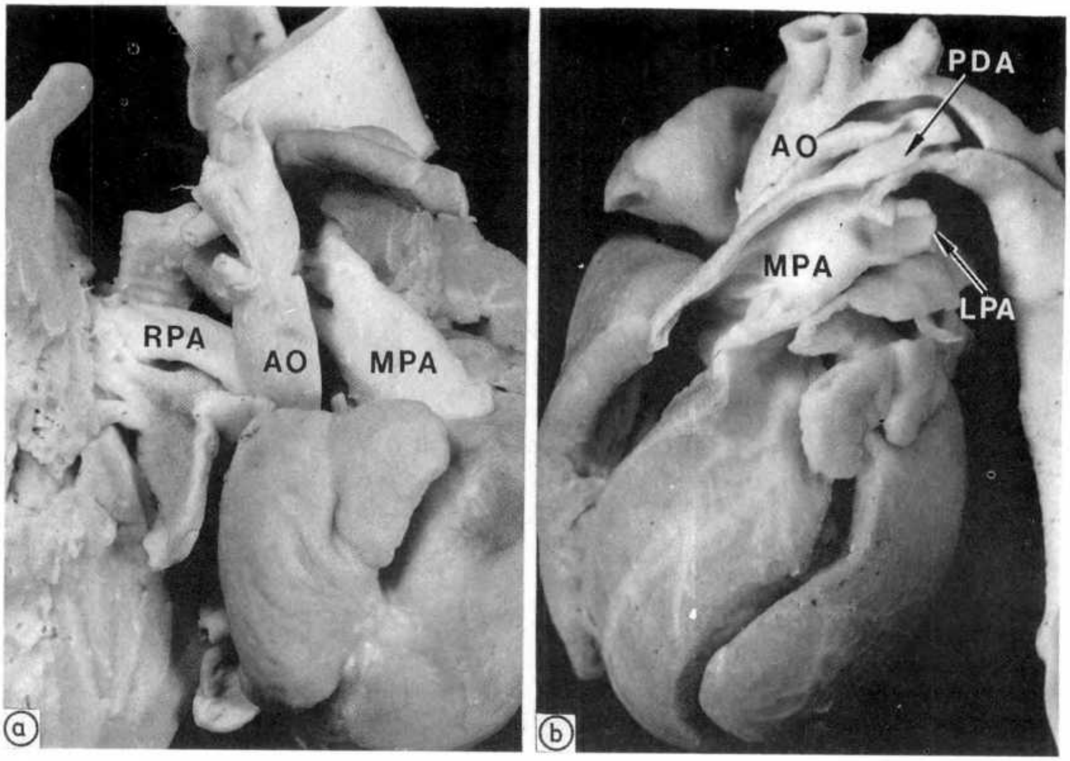


Fig 2 *Necropsy specimen. (a) Anteroposterior view of the right pulmonary artery (RPA) arising from the posterolateral aspect of the ascending aorta (AO) (patient 1). (b) Left lateral view of the left pulmonary artery (LPA) and ductus arteriosus (PDA) arising from the main pulmonary artery (MPA) (patient 1).*

reach the right lung. The anomalous pulmonary artery, which was 4–11 mm in diameter at the hilum, was similar in size to the normally connected contralateral pulmonary artery in those patients without tetralogy of Fallot. In patients with tetralogy of Fallot there was a considerable disparity between the size of the anomalous pulmonary artery and hypoplastic pulmonary artery connected to the right ventricle. There was no stenosis at the origin of the anomalous pulmonary artery and it supplied all segments of the lung in all patients (fig 3a).

Three patients had a right aortic arch—both patients with tetralogy of Fallot and one patient who had an anomalous left pulmonary artery. An aberrant left subclavian artery arising from the descending aorta was found in two of the patients with a right aortic arch (fig 3b).

Patients with tetralogy of Fallot showed a typical intracardiac structure. There was a large malalignment ventricular septal defect with severe infundibular and pulmonary valvar stenosis (fig 4). The pulmonary artery connected to the right ventricle was hypoplastic, measuring from 30% to 60% of the opposite anomalous pulmonary artery. No remnant of a second pulmonary artery arising from the pulmonary trunk was found.

The ductus arteriosus (arterial duct) was patent in the four patients without tetralogy of Fallot. It connected the aorta to the left pulmonary artery in the usual fashion when the arch was left sided (three patients). In the fourth patient, with a right aortic arch and anomalous origin of the left pulmonary artery, the duct passed from the aorta to the right pulmonary artery.

LUNG HISTOPATHOLOGY

Examination of the lungs at necropsy in the two infants (cases 1 and 2) who did not undergo operation showed normal pulmonary vasculature in both lungs. The infants died at 12 (case 1) and 23 (case 2) days of age. Severe vascular changes were seen in the lungs supplied by the anomalous pulmonary artery in both patients who died after repair of tetralogy of Fallot at 25 and 26 months of age. Severe medial and intimal proliferation with focal fibrinoid changes were found in the medium and small sized arteries of the affected

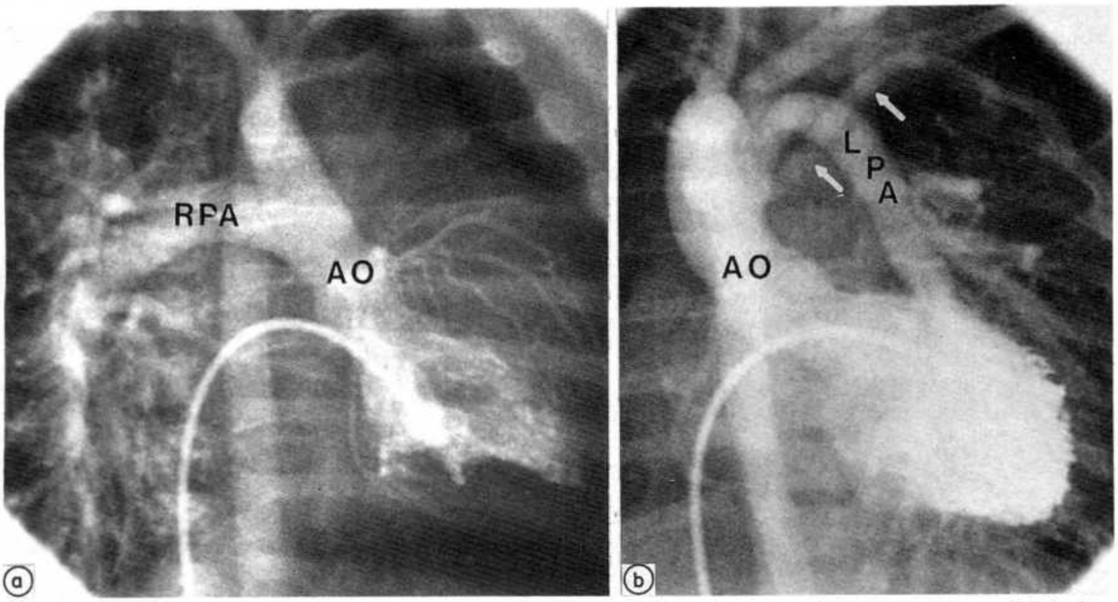


Fig 3 *Left ventriculograms. (a) Right anterior oblique view of anomalous origin of the right pulmonary artery (RPA) from the ascending aorta (AO) (patient 6). (b) Anteroposterior view of another patient with anomalous origin of the left pulmonary artery (LPA) from the ascending aorta (AO), right aortic arch, and distal origin of the left subclavian artery (arrows) (patient 5).*

lung. However, no evidence of pulmonary vascular disease was seen in the lung supplied from the right ventricle, because it was protected by pulmonary valvar and infundibular obstruction.

Biopsy, performed on both lungs of patient 6 who underwent surgical repair at one month and three weeks, showed only mild medial hypertrophy of the muscular pulmonary arteries without intimal or arteriolar changes. The appearances were similar in both lungs.

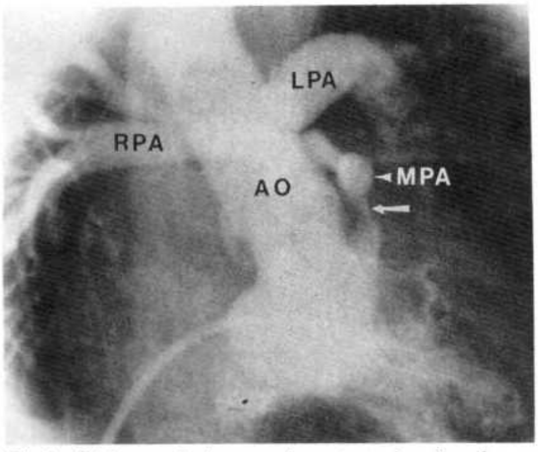


Fig 4 *Right ventriculogrom. Anteroposterior view of anomalous origin of the left pulmonary artery (LPA) from the ascending aorta (AO). The right pulmonary artery (RPA) arises from a hypoplastic main pulmonary artery (MPA) with subpulmonary stenosis (arrow) (patient 3).*

Discussion

Anomalous origin of a pulmonary artery from the ascending aorta is a distinct and well-recognised entity.[1 2] It is a different malformation from pulmonary arteries that originate from the aorta via a ductus arteriosus or are supplied through collaterals between the systemic and pulmonary arteries.[2] The morphology of the anomalous pulmonary artery from the ascending aorta is consistent. The artery arises from the posterolateral wall of the ascending aorta 5–30 mm above the ventriculoarterial junction.[3] It can also arise from the opposite posterior aspect of the ascending aorta.[4] The sizes of the anomalous artery and contralateral pulmonary artery are similar except when there is associated tetralogy of Fallot. Most commonly the right pulmonary artery is anomalously connected.[1 3] Anomalous origin of the left pulmonary artery usually occurs with a right aortic arch, although it has been described with a left aortic arch in association with tetralogy of Fallot.[4 5] Tetralogy of Fallot and arterial ducts are well recognised associations. An anomalous left subclavian artery with a right aortic arch is also seen.

Diagnosis can be made by cross sectional echocardiography,[6 7] when a posterior vessel arising from the ascending aorta and supplying the lung can be visualised in parasternal and suprasternal views. The finding can mimic an aortopulmonary window. Therefore it is important to show that the normal bifurcation of the pulmonary trunk is absent. Subcostal views may be helpful if the anomalous pulmonary artery arises from the lateral aspect of the ascending aorta,[8] but more usually it has a posterior origin. The anomalous pulmonary artery branches normally to supply the lung. Echocardiography and angiography are essential to show the abnormality and associated lesions.

Haemodynamic measurements at catheterisation showed systemic or suprasystemic pressures[9] in the pulmonary artery rising from the right ventricle except when right ventricular outflow tract obstruction coexisted in tetralogy of Fallot. Pulmonary vascular changes when seen at either necropsy or in intraoperative lung biopsy specimens can be correlated with delay in operative repair. Both infants in our series who died within the first month had normal pulmonary vasculature in both lungs. Lung biopsy at 1 month 3 weeks in the infant with suprasystemic pressures in the pulmonary artery that arose from the right ventricle showed only mild medial hypertrophy in the muscular arteries in both lungs. However, both patients with tetralogy of Fallot operated after two years of age had severe unilateral pulmonary vascular changes in the lung supplied by the anomalously connected artery. There was no evidence for pulmonary vascular hypertensive changes in the lungs directly supplied from the right ventricle and protected from excessive pulmonary blood flow by pulmonary and infundibular obstruction. A crossover mechanism of a circulating vasoconstrictor or neurogenic pulmonary hypertension[2 10] from the anomalously supplied lung to the normally supplied lung was given as a possible cause of pulmonary vascular changes in the unaffected lung. However, pulmonary blood flow must clearly be a critical factor in the development of pulmonary vascular disease because patients with tetralogy of Fallot show unilateral changes. Some studies found no significant differences between the lungs on biopsy[10 11] while other studies showed more advanced changes on the non-affected side.[12 13] These changes were attributed to the high flow of fully oxygenated blood in the anomalously supplied lung.

Irrespective of the mechanisms, early surgical intervention, preferably before 12 months of age, is important to prevent the development of irreversible pulmonary vascular disease.[1 14] In patients in whom the anomalous origin of the pulmonary artery is an isolated finding, operative correction should be considered soon after diagnosis and preferably before six months of age, because early changes of pulmonary vascular disease can be identified in the first few months of life. Correction may be possible with or without cardiopulmonary bypass depending upon which side the anomalous pulmonary artery rises and the technical difficulties encountered during operation.[2 3 15] Surgical risk is increased by associated lesions such as tetralogy of Fallot, but successful early surgical repair has been achieved.[16] The hypoplasia of the pulmonary artery connected to the right ventricle will influence the timing of repair but pulmonary vascular hypertensive changes will progress in the anomalously supplied lung if operation is delayed.

It is important to make accurate diagnosis in early infancy, particularly when patients have associated cardiac lesions such as tetralogy of Fallot. This dominating finding may obscure the important associated anomalous origin of one pulmonary artery from the aorta. Anomalous origin of a pulmonary artery from the ascending aorta is a distinct entity, different from other aortopulmonary arterial connections. There is rarely stenosis in the anomalous pulmonary artery and the lung with the anomalous supply is at high risk of the early development of pulmonary vascular hypertensive changes. Delay in recognition of such a lesion may result in fatal pulmonary vascular disease.

References

1 Keane JF, Maltz D, Bernhard WF, Corwin RD, Nadas AS. Anomalous origin of one pulmonary artery from the ascending aorta. *Circulation* 1974;50:588–94.

2 Penkoske PA, Castaneda AR, Fyler DC, Van Praagh R. Origin of pulmonary artery branch from ascending aorta. *J Thorac Cardiovasc Surg* 1983;85:537–45.

3 Kirklin JW, Barratt-Boyes BG. Origin of the right or left pulmonary artery from the ascending aorta. In: *Cardiac surgery*. New York: John Wiley and Sons, 1986:939–44.

4 Calder AL, Brandt PWT, Barratt-Boyes BGT, Neutze JM. Variants of tetralogy of Fallot with absent pulmonary valve leaflets and origin of one pulmonary artery from the ascending aorta. *Am J Cardiol* 1980;46:106–16.

5 Robin E, Silberberg B, Ganguly S, Magnisalis K. Aortic origin of the left pulmonary artery. Variant of tetralogy of Fallot. *Am J Cardiol* 1975;35:324–9.

6 Duncan WJ, Freedom RM, Olley PM, Rowe RD. Two-dimensional echocardiographic identification of hemitruncus: anomalous origin of one pulmonary artery from ascending aorta with the other pulmonary artery arising normally from the right ventricle. *Am Heart J* 1981;102:892–6.

7 King OH, Huhta JC, Gutgesell HP, Ott DA. Two-

dimensional echocardiographic diagnosis of anomalous origin of the right pulmonary artery from the aorta: differentiation from aortopulmonary window. *J Am Coll Cardiol* 1984;4:351–5.

8 Smallhorn JF, Anderson RH, Macartney FJ. Two dimensional echocardiographic assessment of communications between ascending aorta and pulmonary trunk or individual pulmonary arteries. *Br Heart J* 1982;47:563–72.

9 Semb BKH, Bjornstad PG. Correction of isolated anomalous origin of the right pulmonary artery from the ascending aorta. *Thorac Cardiovasc Surg* 1981;29:255–8.

10 Griffiths SP, Levine OR, Anderson DH. Aortic origin of the right pulmonary artery. *Circulation* 1962;25: 73–84.

11 Porter DD, Canent RV, Spach MS, Baylin GJ. Origin of the right pulmonary artery from the ascending aorta. Unusual cineangiographic and pathologic findings. *Circulation* 1963;27:589–93.

12 Weintraub RA, Fabian CE, Adams DF. Ectopic origin of one pulmonary artery from the ascending aorta. *Radiology* 1966;86:666–76.

13 Yamaki S, Suzuki Y, Ishizawa E, Kagawa Y, Horiuchi T, Sato T. Isolated aortic origin of right pulmonary artery. Report of a case with special reference to pulmonary vascular disease in the left and right lungs. *Chest* 1983;3:575–8.

14 Benatar A, Kinsley RH, Milner S, Dansky R, Hummel DA, Levin SE. Surgical correction for one pulmonary artery arising from ascending aorta—report of five cases. *Int J Cardiol* 1987;16:249–55.

15 Sibley YDL, Roberts KD, Silove ED. Surgical correction of anomalous origin of right pulmonary artery from aorta in a four day old neonate. *Br Heart J* 1986;56:98–100.

16 Morgan JR. Left pulmonary artery from ascending aorta in tetralogy of Fallot. *Circulation* 1972;45:653–7.

Br Heart J 1989;62:396–9

Case reports

Recurrent ventricular tachycardia associated with anomalous left coronary artery from the pulmonary artery in a child managed by revascularisation and map-guided endocardial resection

JANET M McCOMB, RICHARD VINCENT,* COLIN J HILTON

*From the Regional Cardiothoracic Centre, Freeman Hospital, Newcastle upon Tyne and *Royal Sussex County Hospital, Brighton*

SUMMARY A 13 year old girl with recurrent ventricular tachycardia that occurred in association with anomalous origin of the left coronary artery from the pulmonary artery is described. Such an arrhythmia has not been described before. Ligation of the anomalous left coronary artery led to more frequent episodes of ventricular tachycardia with evidence of myocardial ischaemia. She was successfully managed by revascularisation (to establish a two coronary system) and map-guided left ventricular aneurysmectomy.

Anomalous origin of the left coronary artery arising from the main pulmonary artery is a rare congenital anomaly that is often fatal in infancy.[1] Myocardial ischaemia is common and infarction may occur, as may mitral regurgitation.[1] The commonest mode of presentation is cardiac failure in infancy, but sudden death may occur both in children and adults with or without previous symptoms.[1-3] In a review of 147 patients, sudden death was reported in 11, occurring after exertion in six.[1] Eight had been symptom free. Sudden death in these patients is thought to be caused by ventricular arrhythmias,[1 2] although such arrhythmias have rarely been recorded.[4 5]

Management is controversial, with both medical and surgical treatment giving poor results,[6] although a comparison was difficult because of bias in the selection of patients.[6] There have been various surgical approaches, although evidence suggests that revascularisation, with establishment of a two coronary system, is the best option.[7 8]

We describe a 13 year old girl who is unusual in several respects. She has survived to adolescence, despite a mortality for this condition in infancy of 80–90%.[1 3] She presented with recurrent ventricular arrhythmias, which increased in frequency after ligation of the anomalous left coronary artery. Further recurrence of arrhythmias was prevented by surgical revascularisation with map-guided ventricular aneurysmectomy.

Case report

This 13 year old girl presented initially at the age of three months when she became cyanosed and dyspnoeic. She was found to be in heart failure with tachycardia, cardiomegaly, and hepatomegaly. She improved gradually after treatment with digoxin, which was subsequently stopped.

She remained well until the age of 11 when during

Requests for reprints to Dr Janet M McComb, Regional Cardiothoracic Centre, Freeman Hospital, Newcastle upon Tyne NE7 7DN.

gymnastics she had an episode of ventricular tachycardia with syncope, chest pain, and dyspnoea (fig 1). After she was admitted to her local hospital an apical systolic murmur was heard. The electrocardiogram showed Q waves in leads I and aVL with loss of R wave amplitude and non specific ST–T wave changes in the lateral chest leads (fig 2). The chest *x* ray showed moderate cardiac enlargement and the echocardiogram showed "slight dilatation of the left ventricle with some hypokinesia." Atenolol 25 mg daily was started and later was increased to 50 mg twice a day. Five months later, after a sudden fright she had a further episode of tachycardia, which terminated spontaneously after 45 minutes. After this, she was able to exercise on the treadmill according to the standard Bruce protocol for 14

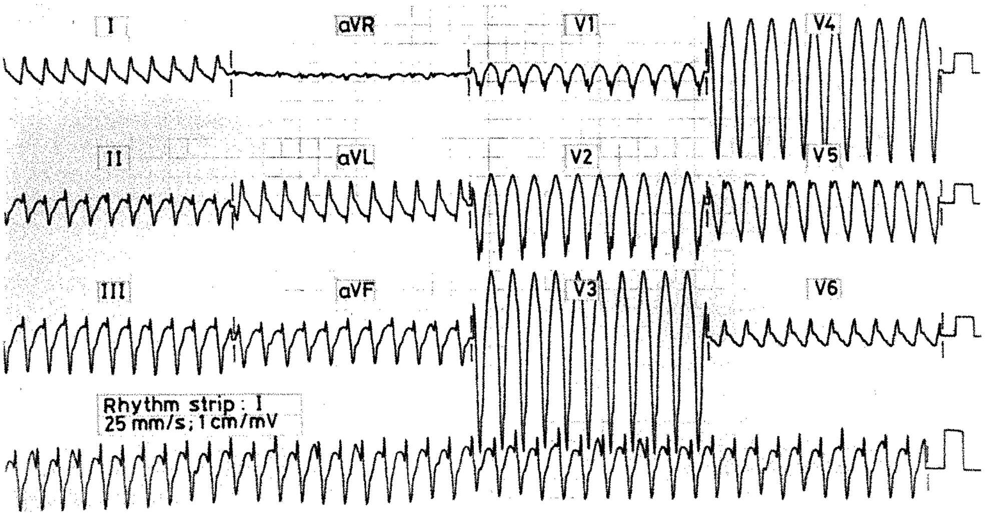


Fig 1 *Electrocardiogram recorded during first episode of ventricular tachycardia.*

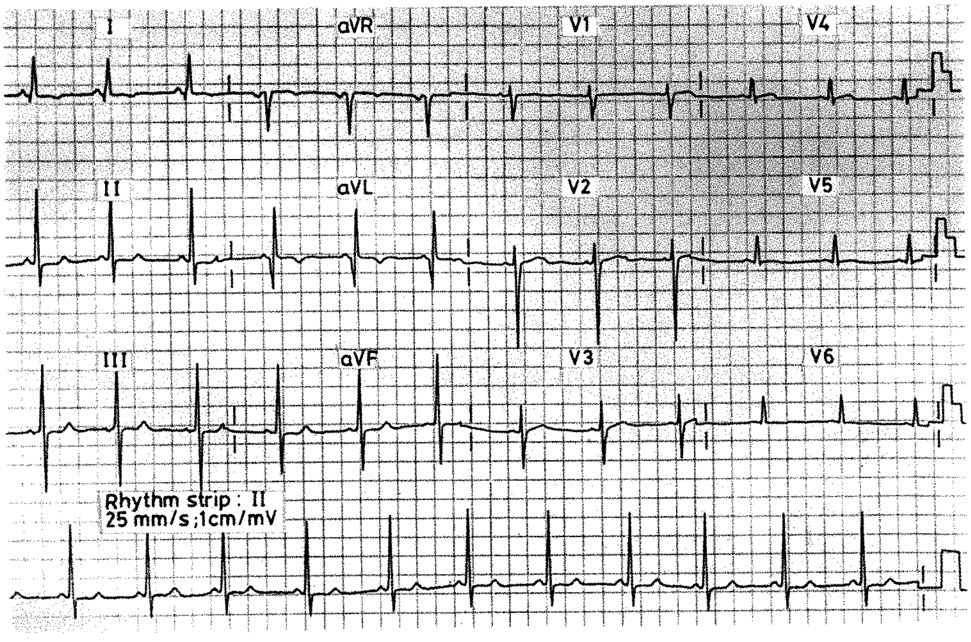


Fig 2 *Electrocardiogram recorded during sinus rhythm.*

minutes, the heart rate rising from 67 to 166 beats per minute. Asymptomatic ST depression developed in the inferior leads and resolved during recovery. Ventricular bigeminy was seen at the termination of exercise. One week later, she complained of mild discomfort in the left arm, legs, and chest, with muscle pains and headache. She went swimming, and after two lengths tachycardia and clutching chest pain developed, which radiated to the back and was eased by glyceryl trinitrate. Runs of ventricular tachycardia were subsequently seen.

She was then referred for invasive studies. Cardiac catheterisation showed an anomalous left coronary artery arising from the main pulmonary artery. The diagnosis was confirmed at operation, when the left coronary orifice was oversewn from within the pulmonary artery. The heart was enlarged and there was a large anteroapical fibrous left ventricular aneurysm. On day 7 an episode of sustained ventricular tachycardia developed and she was treated with flecainide 100 mg twice a day. Three weeks after this she had an episode of palpitation lasting two hours caused by ventricular tachycardia. This was treated by cardioversion. Treatment was changed to mexiletine 100 mg twice a day. Three weeks later she felt "a run of thumps" while cycling. She dismounted, went indoors, and fainted. Her mother described her as deep purple, with a few gasping respirations. She lay still, had no pulse, and no heart beat. Cardiopulmonary resuscitation was started and she recovered within 30 seconds.

She was then transferred to Freeman Hospital. By this time she complained of interscapular pain on exertion and was afraid to exercise. Dipyridamole-thallium scintigraphy confirmed a reversible perfusion defect in the anterior wall, and a coronary angiogram showed a large tortuous right coronary artery. The left coronary artery opacified quickly after injection of the right coronary artery, but its filling was less pronounced than it had been before ligation. No ventricular arrhythmias were induced by programmed ventricular stimulation. At operation, epicardial mapping of both ventricles was performed during normothermic bypass. This identified an area of abnormal electrical activity associated with the apical aneurysm. The left ventricle was then opened through the apical scar and endocardial mapping was performed during sinus rhythm.. This confirmed an area of abnormal electrical activity in the aneurysm. Programmed ventricular stimulation again failed to induce ventricular arrhythmias. The endocardium from which fractionated electrograms were recorded was resected, as was the aneurysm. The left internal mammary artery was grafted to the left anterior descending coronary artery during cold cardioplegia. Postoperatively she made a good recovery. Subsequently, she has done well, growing 11 cm within three months. She is taking no medication, is exercising normally, has no angina, and there has been no recurrence of her arrhythmia.

Discussion

Malignant ventricular arrhythmias are a well recognised sequel of ischaemic heart disease caused by coronary atheroma, but have been less well documented in other forms of myocardial ischaemia. Sudden death has, however, been associated with an anomalous left coronary artery arising from the pulmonary artery,[1-3] and there is evidence that this is more common in adults.[2 3 8] Although it has been suggested that arrhythmias are the cause of sudden death in these patients,[9] such arrhythmias have rarely been described in association with this anomaly.[4 5]

We report an unusual presentation of anomalous left coronary artery, with recurrent sustained ventricular tachycardia and syncope occurring for the first time in adolescence. Heart failure in infancy had resolved with medical treatment, and the patient had been symptom free for 11 years, although there was evidence of silent myocardial ischaemia. Spontaneous resolution of symptoms has been described[10] but is unusual. Her arrhythmias increased in frequency after ligation of the anomalous artery, and ischaemia was again demonstrated. All her symptoms resolved after endocardial resection and revascularisation with the left internal mammary artery.

There has been controversy about the most appropriate treatment, with some advocating medical treatment[6] and some surgical treatment.[7] Various surgical procedures have been recommended, ranging from ligation of the anomalous artery to revascularisation procedures, including direct reimplantation, saphenous vein grafting, and arterial flap repairs.[8] Despite this, surgical results have been described as disappointing.[6] Simple ligation of the anomalous coronary artery is associated with a high mortality,[5 6 11] which has been attributed to ischaemia in the absence of collateral circulation.[7] Ligation leaves a single coronary system, which may lead to subsequent ischaemia. Angina developing some time after ligation has been reported.[11-13] Asymptomatic ischaemia has also been shown by exercise testing[11-14] in approximately half of the few patients so studied. Ligation may also be associated with a higher risk of late sudden death than other surgical procedures.[11] Revascularisation, with the establishment of a two coronary system, is therefore thought to be the best treatment.[7 8 11] Attempts at establishing a two coronary system have had varying results. Early attempts used saphenous vein grafting to the anomalous left coronary artery after ligation.[12] Over 30 patients with saphenous vein grafts have been reported. Grafts were shown to be patent postoperatively in 11 patients,[8 9 12 15 16] and were known to be occluded in five (31%).[8 9 12 13] Various other methods of revascularisation have been described,[7] but none was appropriate in our patient because of the previous ligation. The left internal mammary artery was therefore used to graft the anomalous coronary artery. This technique, not previously described in this condition, satisfactorily established a two coronary system, and may remain patent for longer than a saphenous vein graft.

Map-guided left ventricular endocardial resection was performed in addition to bypass grafting in our patient, as a further antiarrhythmic measure. Others have performed aneurysmectomy[17] or left ventricular resection[7 9] in a few patients, presumably because of heart failure, but a map-guided procedure has not been described before.

This report describes ventricular tachycardia in association with an anomalous left coronary artery, and emphasises the importance of appropriate management of ischaemia in the treatment of this condition.

References

1 Wesselhoeft H, Fawcett JS, Johnson AL. Anomalous origin of the left coronary artery from the pulmonary trunk. Its clinical spectrum, pathology, and pathophysiology based on a review of 140 cases with seven further cases. *Circulation* 1968;**38**:403–25.

2 George JM, Knowlan DM. Anomalous origin of the left coronary artery from the pulmonary artery in an adult. *New Engl J Med* 1959;**261**:993–8.

3 Wilson CL, Dlabal PW, Holeyfield RW, Akins CW, Knauf DG. Anomalous origin of left coronary artery from pulmonary artery. Case report and review of literature concerning teenagers and adults. *J Thorac Cardiovasc Surg* 1977;**73**:887–93.

4 Wright NL, Baue AE, Baum S, Blakemore WS, Zinsser HF. Coronary artery steal due to an anomalous left coronary artery originating from the pulmonary artery. *J Thorac Cardiovasc Surg* 1970;**59**:461–7.

5 Askenazi J, Nadas AS. Anomalous left coronary artery originating from the pulmonary artery. Report on 15 cases. *Circulation* 1975;**51**:976–87.

6 Driscoll DJ, Nihill MR, Mullins CE, Cooley DA, McNamara DG. Management of symptomatic infants with anomalous origin of the left coronary artery from the pulmonary artery. *Am J Cardiol* 1981;**47**:642–8.

7 Vouhe PR, Baillot-Vernant F, Trinquet F, *et al.* Anomalous left coronary artery from the pulmonary artery in infants. Which operation? When? *J Thorac Cardiovasc Surg* 1987;**94**:192–9.

8 Arciniegas E, Farooki ZQ, Hakimi M, Green EW. Management of anomalous left coronary artery from the pulmonary artery. *Circulation* 1980;**62**(suppl 1): 1-180–9.

9 Moodie DS, Fyfe D, Gill CC, *et al.* Anomalous origin of the left coronary artery from the pulmonary artery (Bland-White-Garland syndrome) in adult patients: long-term follow-up after surgery. *Am Heart J* 1983;**106**:381–8.

10 Ihenacho HNC, Singh SP, Astley R, Parsons CG. Anomalous left coronary artery. Report of an unusual case with spontaneous remission of symptoms. *Br Heart J* 1973;**35**:562–5.

11 Bunton R, Jonas RA, Lang P, Rein AJJT, Castenada AR. Anomalous origin of left coronary artery from pulmonary artery. Ligation versus establishment of a two coronary artery system. *J Thorac Cardiovasc Surg* 1987;**93**:103–8.

12 El-Said GM, Ruzyllo W, Williams RL, *et al.* Early and late result of saphenous vein graft for anomalous origin of left coronary artery from pulmonary artery. *Circulation* 1973;**47&48**(suppl III): 2–6.

13 Menahem S, Venables AW. Anomalous left coronary artery from the pulmonary artery: a 15 year sample. *Br Heart J* 1987;**58**:378–84.

14 Shrivastava S, Castenada A, Moller JH. Anomalous left coronary artery from the pulmonary trunk. Long-term follow-up after ligation. *J Thorac Cardiovasc Surg* 1978;**76**:130–4.

15 Laborde F, Marchand M, Leca F, Jarreau M-M, Dequirot A, Hazan E. Surgical treatment of anomalous origin of the left coronary artery in infancy and childhood. Early and late results in 20 consecutive cases. *J Thorac Cardiovasc Surg* 1981;**82**: 423–8.

16 Evans JJ, Phillips JF. Origin of the left anterior descending coronary artery from the pulmonary artery, 3 year angiographic follow-up after saphenous vein bypass graft and proximal ligation. *J Am Coll Cardiol* 1984;**3**:219–24.

17 Turina M, Real F, Meier W, Senning A. Left ventricular aneurysmectomy in a 4-month-old infant. Alternative method of treatment of anomalous left coronary artery. *J Thorac Cardiovasc Surg* 1974;**67**:915–9.

Br Heart J 1989;**62**:400–2

Successful repeat percutaneous transluminal coronary angioplasty after failed coronary artery surgery for left main coronary artery dissection

DAVID R RAMSDALE, PETER M SCHOFIELD

From the Regional Adult Cardiothoracic Unit, Broadgreen Hospital, Liverpool

SUMMARY A 57 year old man required emergency coronary artery bypass surgery after dissection of the left main coronary artery during percutaneous transluminal coronary angioplasty. His symptoms recurred when the vein grafts became occluded. A dilatation device with the lowest profile was used to reduce the need for firm support from the guiding catheter during repeat percutaneous transluminal coronary angioplasty. The repeat procedure was successful in opening up the left circumflex coronary artery.

Dissection of the left main coronary artery is a well recognised but uncommon complication of coronary angiography and percutaneous transluminal coronary angioplasty that requires emergency coronary artery bypass surgery.[1] Dissection can occur when the guiding catheter is deeply engaged in the coronary artery in order to provide support so that the balloon catheter can be advanced across a high grade stenosis during angioplasty.

We describe a patient in whom coronary bypass surgery performed for this complication subsequen-

Requests for reprints to Dr David R Ramsdale, Regional Adult Cardiothoracic Unit, Broadgreen Hospital, Thomas Drive, Liverpool L14 3LB.

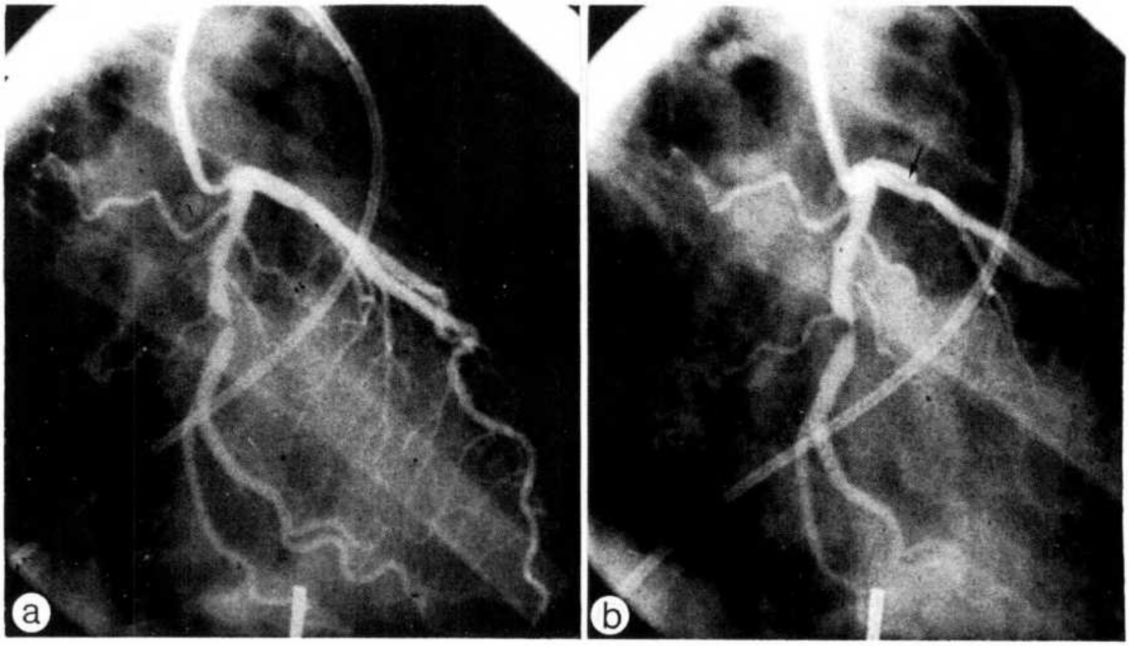


Fig 1 *Angiogram in the right anterior oblique projection showing (a) a severe stenosis in the circumflex artery before coronary angioplasty. (b) During the procedure dissection of the left main coronary artery occurred (arrow).*

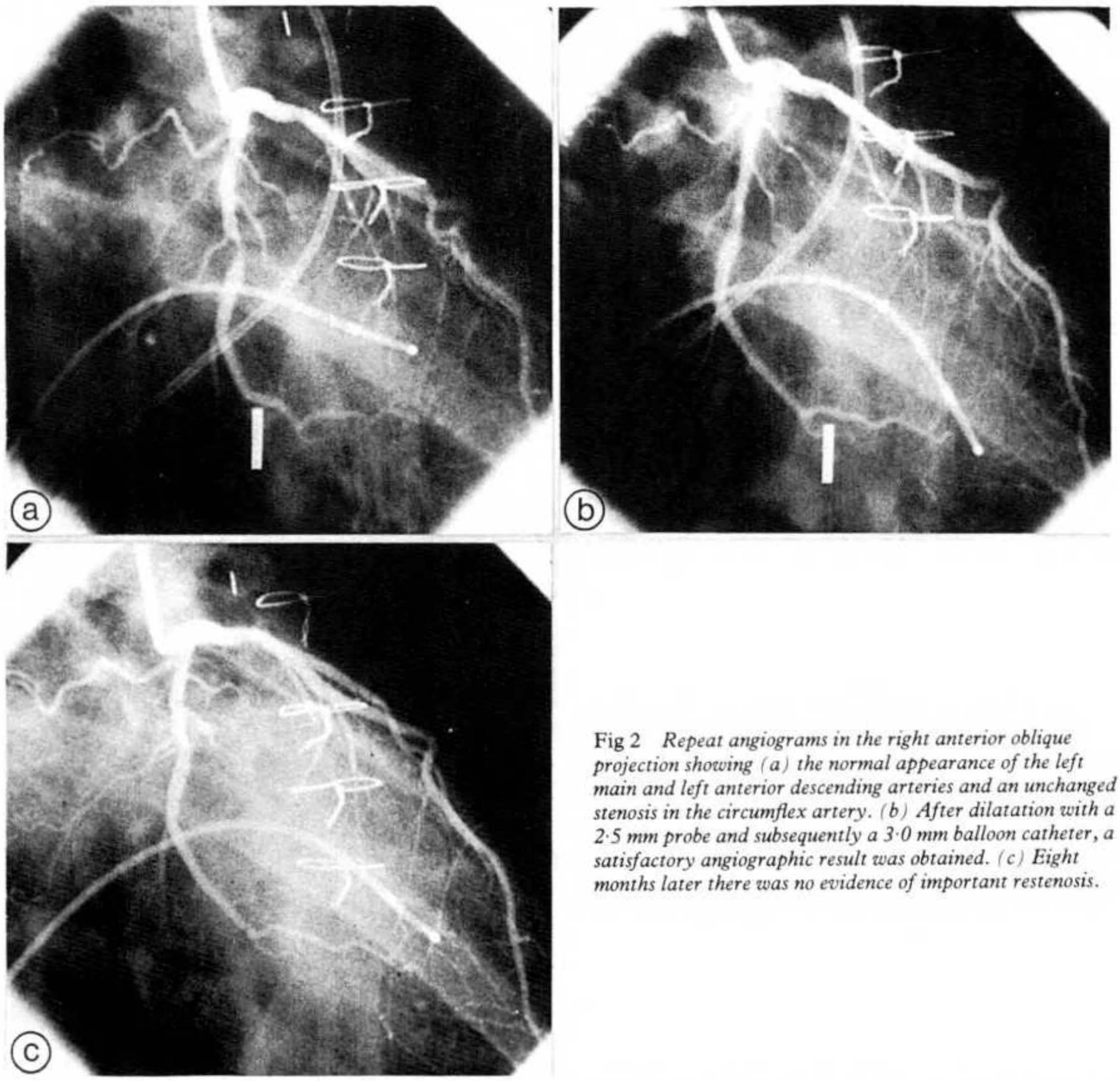


Fig 2 *Repeat angiograms in the right anterior oblique projection showing (a) the normal appearance of the left main and left anterior descending arteries and an unchanged stenosis in the circumflex artery. (b) After dilatation with a 2·5 mm probe and subsequently a 3·0 mm balloon catheter, a satisfactory angiographic result was obtained. (c) Eight months later there was no evidence of important restenosis.*

tly failed but where repeat percutaneous transluminal coronary angioplasty using the lowest profile dilatation device was successful.

Case report

A 57 year old man with a twelve month history of severe angina was found to have an eccentric stenosis of 95% of the diameter of the mid-third of a dominant left circumflex coronary artery (fig 1a). During coronary angioplasty, it was difficult to advance a 3·0 mm low profile "snake" balloon dilatation catheter (balloon profile (BP) 1·3 mm) acoss the stenosis. An attempt to obtain more support for the balloon catheter by deeply engaging an 8F Amplatz soft-tip guiding catheter caused dissection of the left main coronary artery (fig 1b). This rapidly progressed to cause subtotal occlusion of the left coronary artery, chest pain, and anterior ST segment elevation. The patient underwent emergency coronary artery bypass grafting to the left anterior descending, first diagonal, and first and second obtuse marginal coronary arteries.

Within three months of operation, however, he again began to experience angina on moderate effort and subsequently his symptoms increased in frequency and severity despite full medical treatment.

Thirteen months after the operation the patient underwent repeat coronary angiography. This showed occlusion of all of the saphenous vein grafts. Somewhat surprisingly, the left main coronary artery, left anterior descending, and first diagonal arteries appeared to be angiographically normal (fig 2a). However, the severe eccentric stenosis in the left circumflex artery remained. Repeat percutaneous transluminal coronary angioplasty was therefore undertaken.

A further attempt at crossing the stenosis with a 2·5 mm USCI profile plus balloon catheter (BP 0·91 mm) failed because of resistance at the lesion and poor support from the 8F FL 3·5 Judkins soft tip guiding catheter. However, a 2·5 mm USCI probe dilatation device (BP 0·64 mm) crossed the lesion with ease without the need for deep engagement of the guiding catheter and a satisfactory dilatation was achieved. We advanced a 3·0 mm balloon catheter (USCI low profile plus, BP 0·97 mm) across the residual lesion using a conventional 0·36 mm ACS high torque floppy guide wire. A satisfactory angiographic result was achieved after dilatation (fig 2b).

The patient was active and free of angina six months later. At eight months there was no angiographic evidence of restenosis (fig 2c).

Discussion

Dissection is more likely to occur with 9F Judkins and with Amplatz shaped guiding catheters.[2] Soft tipped catheters have been produced to help minimise the risk but they are unlikely to eliminate this complication completely. Moreover, this case highlights the advantage of the extremely low profile of dilatation devices such as the USCI probe, which have more recently become available. This catheter may assist safe crossing of severely stenosed, eccentric lesions situated distally in the coronary arteries without the need for deep engagement of the guiding catheter. However, having chosen this catheter, the operator currently has to accept that unless the ratio of balloon:vessel size is optimal, the lesion may need to be recrossed to improve the final angiographic result—a procedure that still causes concern especially when intimal dissection is visible. The SciMed DGW (Dilating Guide Wire – with a 1·5 mm polyolefin balloon (BP 0·43 mm)), which can be passed through an appropriately sized TRAC^R balloon catheter, is designed to help overcome this problem.

Finally, our case shows one possible course of left main coronary artery dissection treated by coronary artery bypass surgery—that is subsequent healing and normalisation of the vessel.

We are not aware of any previous reports of percutaneous transluminal coronary angioplasty to the native left coronary artery after left main coronary artery dissection. If technically possible, this procedure is clearly preferable to repeat bypass surgery.

References

1 Dorros G, Cowley MJ, Simpson J, *et al.* Percutaneous transluminal coronary angioplasty: report of complications from the National Heart, Lung and Blood Institute PTCA Registry. *Circulation* 1983;67:723–30.

2 Ischinger T. *Practice of coronary angioplasty.* Berlin, Heidelberg: Springer Verlag, 1986:135, 148, 252.

Br Heart J 1989;62:403–5

Spontaneous displacement of a pacemaker electrode and its subsequent successful reimplantation

JOHN GIALAFOS, ANASTASIOS THEOPHILIS, GEORGE SIAMAS

From B Department of Cardiology and Cardiac Department, University of Athens Medical School, Hippokration Hospital, Athens, Greece

SUMMARY A case of what was assumed to be twiddler's syndrome was caused by spontaneous twisting and displacement of the electrode on the fortieth postoperative day. The pacemaker had not been manipulated by the patient, the pocket was tight, and the proximal electrode was well secured. The complication was managed successfully by reimplanting the same electrode after stiffening the lead near the generator with a portion of the stylet.

Pacemaker twiddler's syndrome was first described by Bayliss *et al* in 1968.[1] They reported a case in which the pulse generator had twisted in its subcutaneous pocket, apparently because it had been manipulated by the patient. This twisting led to retraction of the electrode into the superior vena cava and consequent interruption of pacing. Since then, there have been several reports of similar cases with various access routes (transvenous, epicardial),[2-4] types of leads (unipolar, bipolar),[3] and pulse generator pocket positions (pectoral, abdominal)[3 4] and comparisons of conventional pacemakers and implantable internal automatic cardioverter defibrillators.[5]

We describe a patient in whom the transvenous ventricular pacing electrode became displaced by spontaneous twising of the electrode. We managed this complication in a new way.

Case report

A 68 year old woman (weight 67 kg, height 1·61 m) underwent implantation of a Medtronic 5941 VVI pacemaker with target tip unipolar electrode (Medtronic-4011-58) because of symptomatic 2:1 atrioventricular block. The pacing threshold was 0·4 V or 0·8 mA with 450 Ω resistance and satisfactory endocardial potentials. The electrode was attached to the surrounding tissue with three double silk sutures (Mersilik 3·5), according to the standard practice of our pacing unit. The position and functioning of the pacing system were entirely satisfactory initially and on the second examination 20 days later (fig 1a).

On the fortieth postoperative day, however, the patient was brought to the clinic because of loss of pacing capture. The *x* ray (fig 1b) showed that the electrode tip was displaced into the superior vena cava and that the lead was twisted near to the generator. The position and orientation of the generator were almost exactly as they had been at the time of implantation. The patient consistently denied touching or manipulating the area of the pacemaker pocket.

On reoperation, the pacemaker pocket was found to be tight around the generator but there were several twists in the electrode lead close to the generator, despite the double sutures still being in place. Because it was difficult to withdraw the electrode past the junction of the subclavian and cephalic veins, we decided on a novel solution to the problem. We reimplanted the same electrode, after inserting approximately half of the soft stylet (35 cm) into the part of the lead nearest the generator. Thus the distal part of the stylet, which we had curved slightly to assume its final position, was in the superior vena cava, while the proximal end coincided with the proximal end of the electrode, which was screwed into the generator. (Cutting the stylet with scissors had left a slight flange around what became the proximal end, and this prevented the stylet sliding towards the electrode tip.) In this way, the proximal part of the electrode was stiffened and made more resistant to twisting (fig 2).

Discussion

As first described by Bayliss *et al.*[1] the lead displacement in pacemaker twiddler's syndrome is due to a capstan effect produced by the pulse generator's

Requests for reprints to Dr John Gialafos, 17–19 Ploutarchou Street, 106 75 Athens, Greece

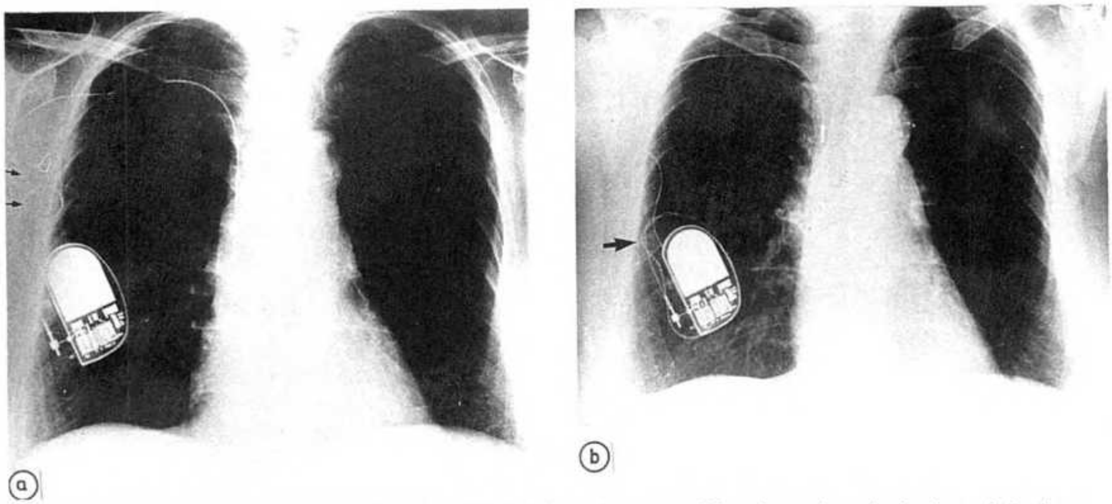


Fig 1 *(a) Radiograph showing the satisfactory position of the pacing system. Note the two loops in the electrode lead (arrows). (b) Radiograph showing displacement of the electrode tip to the superior vena cava and twisting of the electrode (arrow) close to the pacemaker. The position and orientation of the generator are almost identical with those shown in (a).*

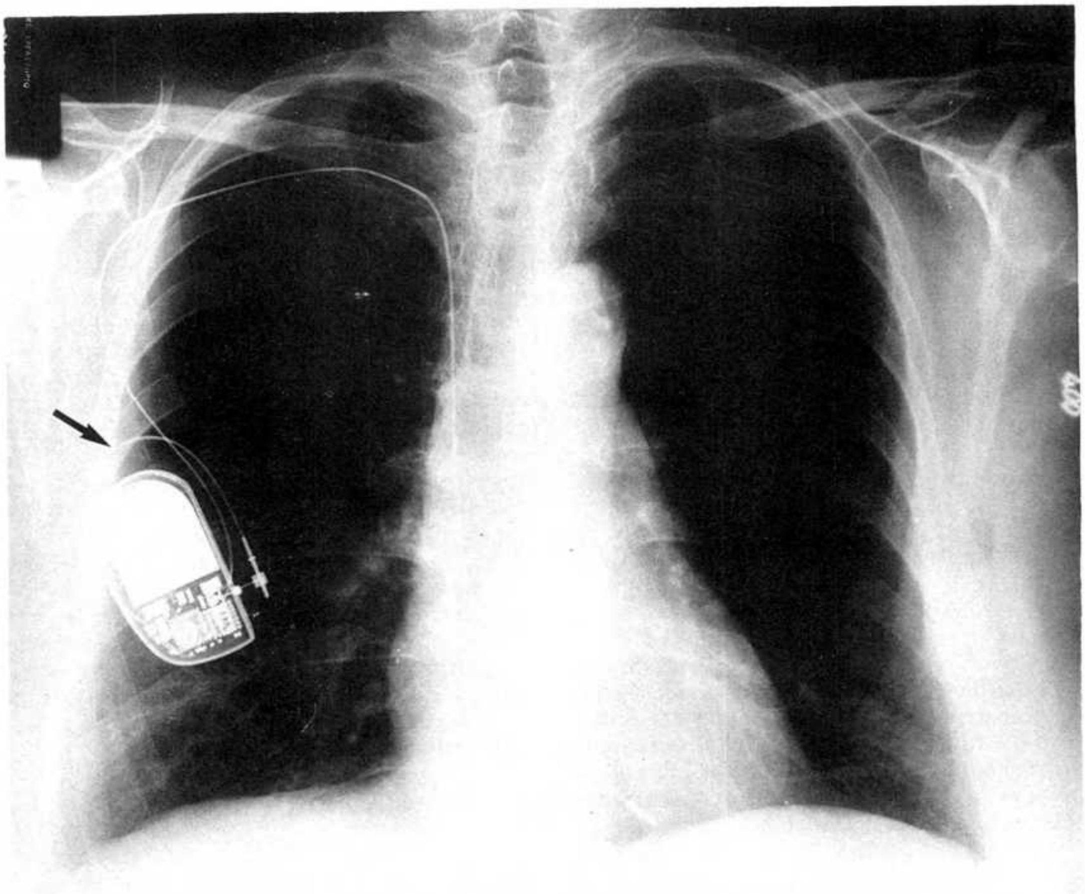


Fig 2 *Radiograph after reimplantation of the electrode in the apex. The proximal part of the electrode forms one large loop (arrow) because of its extra stiffness, in contrast with the two loops formed by the original, more flexible electrode, as shown in fig 1a.*

rotation within a capacious pulse generator pocket. According to Smyth and Millette, this syndrome is found in obese patients, in whom a loose generator pocket tends to form.[6] Spontaneous rotation of the pulse generator may then occur, as a result of arm movement, when there is a loose pocket, when the generator has not been fixed firmly in place, or when a single fixation suture has been used, which then provides a fulcrum around which the pulse generator can rotate.

In our case the patient was not obese, there was no slackness in the generator pocket, and the patient consistently denied fiddling with the pocket.

The *x* ray showed that the pulse generator was in almost exactly the same position as on implantation. On reoperation, we found that the pocket fitted tightly around the generator, with no fluid accumulation, and the three double securing sutures were clearly identifiable.

We concluded that the electrode was dislodged by spontaneous twisting, which retracted the electrode. This case provides strong grounds for believing that the term "pacemaker twiddler's syndrome" is not always apt. We agree with Smyth and Millette[6] that this term should be abandoned.

It is generally believed that when a pacemaker lead is disturbed in this way it should be removed and replaced or fixed and replaced by a new lead.[6] In our patient it was impossible to remove the original electrode. Because we strongly believed that the lead twisting was spontaneous and that the lead itself was undamaged, we decided to reimplant the same electrode, leaving a large part of the stylet inside the lead and connected with it to the generator. The stylet is quite flexible and we did not expect that the end of the stylet would damage the lead, especially as the stylet was shaped appropriately before insertion. In this way we stiffened the electrode as far as the superior vena cava, sufficiently to preclude further twisting. On reimplantation, the threshold was only 0·3 V or 0·7 mA with 472 Ω resistance, confirming that the electrode was in good condition. The pacemaker was not given any extra support.

The follow up over eight months has been uneventful, with no signs of lead damage or displacement, and the patient is doing well.

References

1 Bayliss CE, Beanlands DS, Baird RJ. The pacemaker-twiddler's syndrome: a new complication of implantable transvenous pacemakers. *Can Med Assoc J* 1968;99:371–3.
2 Stamford W, Coyle FL, Dooley BN, *et al.* Transvenous pacemaker failure: migration of catheter lead by patient manipulation. *Ann Thorac Surg* 1969;5:162–4.
3 Meyer JA, Fruehan CT, Delmonico JE. The pacemaker twiddler's syndrome—a further note. *J Thorac Cardiovasc Surg* 1974;67:903–7.
4 Guharay BN, Ghose JC, Majumdar H, Basu AK. The pacemaker-twiddler's syndrome: another disadvantage of abdominal implantation of pulse generators. *Br J Surg* 1977;64:655–60.
5 Veltri EP, Mower M, Read PR. Twiddler's syndrome: a new twist. *PACE* 1984;7:1004–9.
6 Smyth NPD, Millette ML. Complications of pacemaker implantation. In: Barold SS, ed. *Modern cardiac pacing* Mount Kisco, New York: Futura, 1985: 257–75.

Br Heart J 1989;62:406–8

Congenital fistula between the left ventricle and coronary sinus: elucidation by colour Doppler flow mapping

J P GNANAPRAGASAM, A B HOUSTON, S LILLEY

From the Departments of Cardiology and Child Health, Royal Hospital for Sick Children, Glasgow

SUMMARY A fistula between the left ventricle and the coronary sinus was diagnosed by Doppler echocardiography and confirmed by cardiac catheterisation in a symptom free child who presented with clinical signs of mitral regurgitation. A similar abnormality has been reported after repeated mitral valve replacement and after myocardial infarction but a congenital fistula of this type has not been described before.

Congenital abnormalities of the coronary sinus are uncommon. They include abnormal systemic or pulmonary venous drainage into the coronary sinus, fistulas between the coronary artery and coronary sinus, absence of the coronary sinus, atresia of the coronary sinus ostium,[1] and coronary sinus aneurysms.[2 3] The development of an iatrogenic fistula between the left ventricle and the coronary sinus is a recognised surgical complication after repeated prosthetic mitral valve replacement.[4 5] An acquired fistula has also been reported as a complication of acute myocardial infarction.[6] We report the case of a child with a congenital fistula between the left ventricle and the coronary sinus, a congenital abnormality that has not been described before.

Case report

A 20 month old girl was found to have an asymptomatic heart murmur on routine examination. Her previous history and family history were unremarkable. Physical examination showed a well nourished child with no cyanosis or clubbing and normal pulses. The apex beat was not displaced and there was no precordial thrill. Auscultation showed normal heart sounds with a grade 2/6 long systolic murmur best heard over the apex and radiating to the axilla and back. There was no other murmur. A clinical diagnosis of mitral regurgitation was made.

Electrocardiography was normal. Cross sectional imaging showed normal mitral valve leaflets and papillary muscle attachments. Stand alone continuous wave Doppler examination showed a high velocity systolic jet (velocity 4·2 m/s, equivalent to a pressure gradient of 70 mm Hg) in the region of the mitral valve, which was interpreted as being in keeping with the clinical diagnosis of mild mitral regurgitation.

Review when she was five years old showed that she was symptom free with no change in the physical signs. Echocardiography was performed with a Vingmed CFM 700 system with duplex pulsed and continuous wave and colour Doppler flow mapping. Colour Doppler clearly showed a high velocity jet from the left ventricle through its posterior wall into an enlarged coronary sinus (fig 1). Doppler examination at a high frequency of pulse repetition and with the sample volume placed over the jet seen on colour mapping confirmed a systolic jet with a velocity of about 4 m/s (pressure difference 64 mm Hg). The spectral record showed both a fixed obstructive signal and a dynamic one, which indicated increasing obstruction during systole.

Subsequent careful ultrasound examination showed that when the scanning plane was tilted to the right, the medial part of the coronary sinus could be shown to be dilated. Colour Doppler flow mapping showed a communication between the left ventricle and the coronary sinus. There was no evidence of mitral regurgitation or other abnormality.

Cardiac catheterisation was undertaken to confirm this unusual abnormality. Left ventricular angiocardiography produced immediate opacification of the coronary sinus (fig 2a) before filling of the coronary arteries had occurred. The coronary arteries were normal. The cardiac veins drained normally into an aneurysmally dilated coronary sinus (fig 2b). The oxygen saturation in the peripheral part of the coronary sinus was 38% and in the dilated medial part it was 95%. This indicated left to right

Requests for reprints to Dr J P Gnanapragasam, Royal Hospital for Sick Children, Yorkhill, Glasgow G3 8SJ.

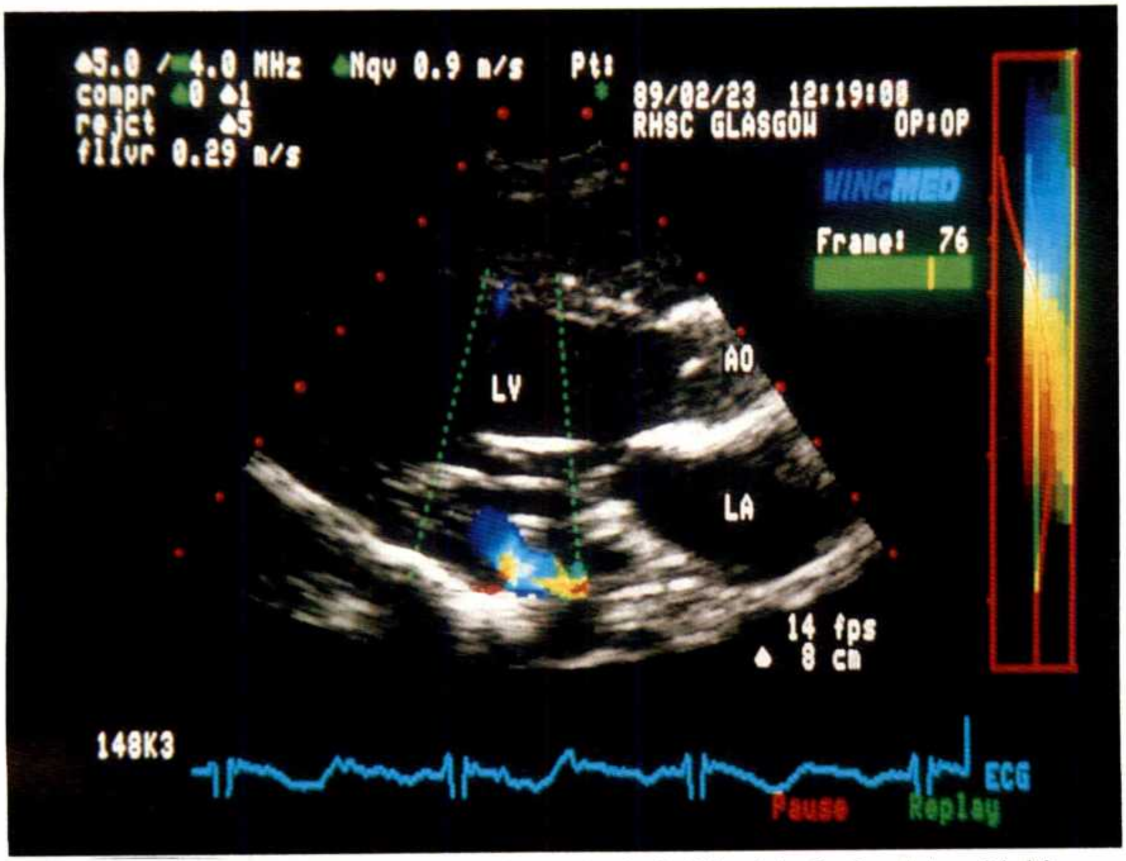


Fig 1 *Parasternal long axis view with colour Doppler flow mapping showing high velocity flow from the base of the left ventricle into the coronary sinus, which is dilated. LV, left ventricle; LA, left atrium; Ao, aorta.*

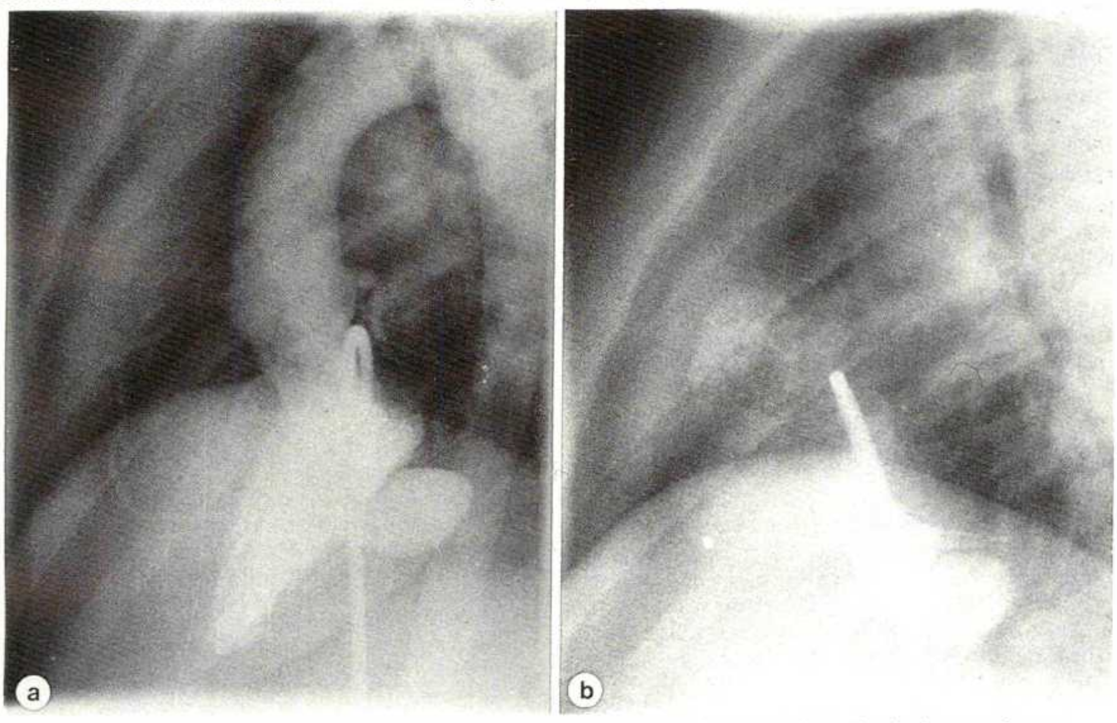


Fig 2 *(a) Left ventricular angiocardiogram showing filling of the aneurysmal coronary sinus. (b) Angiogram after an injection of contrast into the coronary sinus.*

flow into the coronary sinus, but there was no rise in oxygen saturation in the pulmonary artery, indicating that there was no haemodynamically significant left to right shunt. Contrast echocardiography through the catheter placed in the left ventricle showed an immediate appearance of contrast in the coronary sinus and then in the right atrium, but not in the left atrium. These investigations conclusively proved the presence of a communication between the left ventricle and the coronary sinus.

Electrophysiological studies were undertaken because of the reported high incidence of arrhythmias and sudden death associated with coronary sinus aneurysm.[3] They showed no evidence of an accessory pathway between the right atrium and right ventricle.

Discussion

The coronary sinus lies in the posterior atrioventricular groove and when it is dilated it can be imaged with echocardiography in the parasternal long axis view.[7] Dilatation of the coronary sinus is usually caused by increased blood flow into it and may be the result of a coronary arteriovenous fistula or anomalous pulmonary or systemic venous drainage.[1] Although the shunt was small in our patient, the high pressure flow from the left ventricle may have caused dilatation of the proximal coronary sinus. Aneurysmal dilatation of the coronary sinus may also occur as an isolated defect without a shunt into the sinus.[2,3]

An acquired fistula between the left ventricle and the coronary sinus can occur after repeated mitral valve replacement[4,5] and after myocardial infarction.[6] This rare occurrence can be explained by the close anatomical relation between the coronary sinus and the left ventricle. Because the coronary sinus arises from the left horn of the sinus venosus it should have no communication with the left ventricle, which has a quite separate embryological origin. A fistula can occur from the left ventricle to a coronary artery, and from a coronary artery to the coronary sinus; this was the basis of the only similar case reported, a patient with aortic valve atresia, left ventricular hypoplasia, intact atrial septum, and dilated intramyocardial sinusoids,[8] which is very different from the present case. Another possible explanation for this unusual fistula is that a primary congenital aneurysm of the coronary sinus may have subsequently ruptured into the left ventricle creating a left ventricle to coronary sinus fistula.

There are four published reports of coronary sinus aneurysm[2,3]; one was a chance diagnosis in a baby undergoing cardiac catheterisation and the other three were diagnoses made at necropsy in young patients who died suddenly. These three patients had a history of tachycardia and accessory atrioventricular pathways were found in two of them. Our patient, however, has no history of arrhythmias and electrophysiological studies were normal.

In view of the high pressure shunt into the coronary sinus and the possibility of further dilatation and extracardiac rupture of the aneurysm we decided that the fistula should be closed surgically at a later date.

In this case the suspicion of an abnormality was first raised by the unusual position of the abnormal high velocity jet on colour Doppler and careful examination of the area identified the fistula. Without this investigation the murmur would probably have been regarded as a consequence of mild mitral regurgitation and further investigation would not have been undertaken. If Doppler studies are not available the lesion should be suspected where there are clinical signs of mitral regurgitation in a patient with dilatation of the medial part of the coronary sinus. The routine use of colour Doppler flow mapping may identify further patients with similar lesions.

JPG is supported by a grant from the Equipment Evaluation Committee of the Scottish Home and Health Department.

References

1 Mantini E, Grondin CM, Lillehei CW, Edwards JE. Congenital anomalies involving the coronary sinus. *Circulation* 1966;**33**:317–27.

2 Ho SY, Gupta I, Anderson RH, Lendon M, Kerr I. Aneurysm of the coronary sinus. *Thorax* 1983;**38**:686–9.

3 Gerlis LM, Davies MJ, Boyle R, Williams G, Scott H. Pre-excitation due to accessory sinoventricular connexions associated with coronary sinus aneurysms: a report of two cases. *Br Heart J* 1985;**53**:314–22.

4 Morritt GN, Jamieson MPG, Irving JB, Marquis RM, Walbaum PR. Development of left ventricular-coronary sinus fistula following replacement of mitral valve prosthesis. *J Thorac Cardiovasc Surg* 1978; **76**:381–4.

5 Miller DC, Schapira JN, Stinson EB, Shumway NE. Left ventricular-coronary sinus fistula following repeated mitral valve replacements. *J Thorac Cardiovasc Surg* 1978;**76**:43–5.

6 Mahfood SS, Watson DC, Di Sessa TG, Nunn SL, Ratts TE. Acquired left ventricular to coronary sinus fistula: an unusual complication of acute myocardial infarction. *Ann Thorac Surg* 1987;**44**:550–1.

7 Snider AR, Ports TA, Silverman NH. Venous anomalies of the coronary sinus: detection by M-mode, two-dimensional and contrast echocardiography. *Circulation* 1979;**60**:721–7.

8 Ragis G, Bloemendaal RD, Kanyah VI, Edwards JE. Aortic atresia and premature closure of foramen ovale. Myocardial sinusoids and coronary arteriovenous fistula serving as outflow channel. *Am Heart J* 1965;**70**:476–80.

Br Heart J 1989;**62**:409–10

Heart transplantation for Churg-Strauss syndrome

DAVID THOMSON,* HASSAN CHAMSI-PASHA,† P HASLETON‡

*From the †Department of Medicine, Hope Hospital, and Departments of *Cardiothoracic Surgery and ‡Pathology, Regional Cardiothoracic Centre, Wythenshawe Hospital, Manchester*

SUMMARY A patient with heart failure caused by Churg-Strauss syndrome was successfully treated with transplantation. The case was unusual because there was little evidence of Churg-Strauss syndrome in the lung. The patient remains well on standard transplant immunotherapy.

Churg-Strauss syndrome was first described in 1951.[1] It is characterised by blood and tissue eosinophilia and disseminated necrotising vasculitis in asthmatic patients. Heart failure occurs in 47% of patients and accounts for nearly half the deaths.[2] We report a 22 year old man with Churg-Strauss syndrome in whom heart failure developed necessitating heart transplantation. To our knowledge, this is the first report to describe heart transplantation in a patient with this syndrome.

Case report

A 22 year old man was first seen in July 1986 complaining of breathlessness and wheezing. The chest radiograph showed bilateral interstitial lung opacities and he had pronounced eosinophilia ($7 \cdot 7 \times 10^9/l$). Pulmonary eosinophilia was diagnosed and resolved when he was treated with oral steroids and bronchodilators. He remained well on 10 mg/day of prednisolone until July 1987 when he was admitted to hospital with a sudden onset of cough and breathlessness. The radiograph (figure) showed considerable cardiomegaly and pulmonary oedema and the electrocardiogram showed low voltage complexes. Echocardiography showed biventricular dilatation with a small pericardial effusion. The ejection fraction was estimated to be 15%. The eosinophil count was $3 \times 10^9/l$. The dose of steroids was increased and the eosinophilia resolved within three days. Cardiac catheterisation showed a pulmonary capillary wedge pressure of 18 mm Hg and a mean pulmonary artery pressure of 24 mm Hg. Myocardial muscle biopsy showed prominent foci of young fibroblastic tissue with necrotic and hypertrophied myocytes and an infiltrate of lymphocytes, plasma cells, and eosinophils. No vasculitis was seen. Two months later the heart failure worsened. Echocardiography showed further dilatation of the heart chambers and impairment of left ventricular function. Serum concentrations of urea and creatinine were 7·1 mmol/l and 0·11 mmol/l respectively, with a creatinine clearance of 113 ml/min. Microscopical examination of urine did not show haematuria, casts, or proteinurea. In October 1987, he was transferred to Wythenshawe Hospital. He was anuric and had a mean blood pressure of 30 mm Hg, that improved during treatment with adrenaline, intra-aortic balloon counterpulsation, and ventilation. Two days later, orthotopic cardiac transplantation was performed.

The excised heart weighed 340 g and there was dilatation of all chambers. The right ventricle

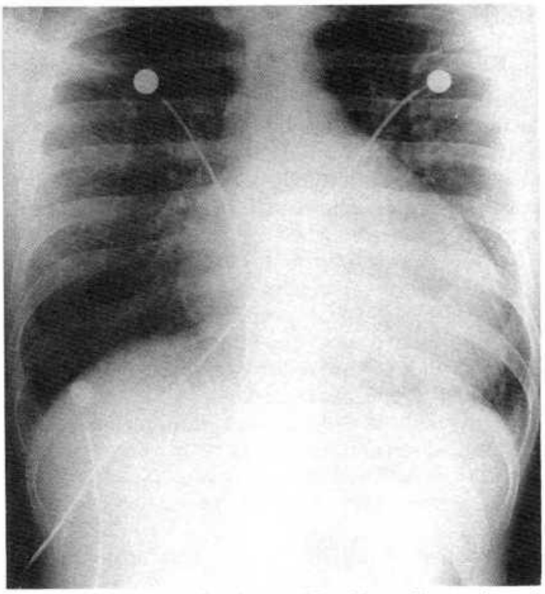


Figure *Chest x ray showing considerable cardiomegaly and pulmonary oedema.*

Requests for reprints to Mr David Thomson, FRCS, Department of Cardiothoracic Surgery, Wythenshawe Hospital, Manchester M23 9LT.

weighed 83 g and the left 213 g. The myocardium had mottled yellow/white foci. The coronary arteries were macroscopically normal.

Fibrinoid necrosis with some giant cells was seen in some intramyocardial vessels. There was arteritis in the right coronary artery. All the cardiac valves were histologically normal. Subendocardial fibrinoid necrotic foci were seen especially in the left atrium and ventricle, as well as foci of fibrosis and associated hypertrophy. A mild eosinophilic infiltrate was present. A lung biopsy specimen showed an interstitial infiltrate of lymphocytes, plasma cells, and occasional neutrophils. No vasculitis was identified.

Postoperatively, after perioperative antithymocyte globulin, he was treated with cyclosporin, azathioprine, and steroids. Three weeks after transplantation, a fever and diffuse pulmonary shadowing developed. The donor heart came from a cytomegalovirus seropositive person and so we treated our patient for cytomegalovirus pneumonitis. He recovered after treatment with gancyclovir and cytomegalovirus immunoglobulin. Two months after discharge from hospital he was readmitted with cough and breathlessness and eosinophilia (2×10^9/l). A cardiac biopsy specimen did not show rejection and we thought he had had a relapse of Churg-Strauss syndrome. The maintenance dose of steroids was increased; his condition improved and the eosinophil count returned to normal. The patient remains well twelve months after transplantation.

Discussion

Churg-Strauss syndrome is a rare disorder characterised by asthma, large numbers of eosinophils in the blood and tissue, angiitis, and necrotising granulomatous lesions in other organs such as the heart, lungs, nervous system, kidneys, spleen, skin, muscles, and gastrointestinal tract.[1-3] When Lanham *et al* reviewed published reports they found 138 patients with this syndrome.[2] The mean age of onset is 44 years with male to female ratio of 1·3:1.

At necropsy the heart is often found to be affected in Churg-Strauss syndrome and the cardiac manifestations include cardiac failure, myocardial infarction, hypertension, and pericarditis.[1-4]

Myocardial scarring, inflammation, cardiac dilatation, and adherent mural thrombosis were reported.[1] In addition, eosinophilic endomyocarditis leading to advanced restrictive cardiomyopathy has been described.[5]

Our patient developed clinical, echocardiographic, and pathological features of congestive cardiomyopathy with multiple ventricular thromboses. The echocardiographic diagnosis of multiple ventricular thrombi in a patient with Churg-Strauss syndrome has not previously been reported.

If untreated, the prognosis is poor with a five year survival rate of 25%. With immunosuppressive treatment a five year survival rate of 62% was reported.[3] In our patient intractable heart failure developed despite conventional treatment. Cardiac transplantation was the only remaining option.

The fact that a "relapse" after transplant was felt to be due to resurgence of Churg-Strauss syndrome gives rise to the question of whether standard triple immunosuppressive treatment can be adequately targeted against such a syndrome. Because Churg-Strauss syndrome is basically caused by a humorally mediated response, we would not expect that cyclosporin with its specific action against T lymphocytes would have much effect on the suppression of Churg-Strauss syndrome. The single episode of relapse was successfully treated by increasing the dose of steroids and it may be that the best combination is azathioprine and cyclosporin, with lower doses of cyclosporin than usual, together with indefinite treatment with steroids, which currently we stop after a year.

As yet there is no evidence that the transplanted heart has been affected by the Churg-Strauss syndrome.

D T is Wellcome Transplant Fellow at Wythenshawe Hospital. We thank the following for their help and for permission to report this case. A N Rahman (consultant surgeon, Wythenshawe Hospital), N H Brooks (consultant cardiologist, Wythenshawe Hospital), A Holmes (renal physician, Hope Hospital), W P Stephen (consultant physician, Park Hospital).

References

1 Churg J, Strauss L. Allergic granulomatosis, allergic angiitis and periarteritis nodosa. *Am J Pathol* 1951; **27**:277–301.

2 Lanham JG, Elkon KB, Pusey CD, Hughes GR. Systemic vasculitis with asthma and eosinophilia: a clinical approach to the Churg-Strauss syndrome. *Medicine (Baltimore)* 1984;**63**:65–81.

3 Chumbley LC, Harrison EG Jr, DeRemee RA. Allergic granulomatosis and angiitis (Churg-Strauss syndrome): report and analysis of 30 cases. *Mayo Clin Proc* 1977;**52**:477–84.

4 Davison AG, Thompson PJ, Davies J, Corrin B, Turner-Warwick M. Prominent pericardial and myocardial lesions in the Churg-Strauss syndrome (allergic granulomatosis and angiitis). *Thorax* 1983; **38**:793–5.

5 Lanham JG, Cooke S, Davies J, Hughes GRV. Endomyocardial complication of the Churg-Strauss syndrome. *Postgrad Med J* 1985;**61**:341–4.

Br Heart J 1989;**62**:411–4

British cardiology

The Randomised Intervention Treatment of Angina (RITA) Trial protocol: a long term study of coronary angioplasty and coronary artery bypass surgery in patients with angina

R A HENDERSON, for the Randomised Intervention Treatment of Angina Trial*

SUMMARY The Randomised Intervention Treatment of Angina (RITA) Trial is a prospective, randomised study to compare the short term and long term effects of percutaneous transluminal coronary angioplasty and coronary artery bypass surgery. During the study a register of patients undergoing coronary arteriography at the fourteen participating centres is being maintained to assess the overall context of patient recruitment. Patients with arteriographically proven coronary artery disease are considered for the trial if the participating cardiologist and surgeon agree that equivalent revascularisation could be achieved by either treatment method. Patients who satisfy the trial entry criteria are randomised to treatment by coronary angioplasty or coronary artery bypass surgery, with prospective stratification into groups with one, two, or three treatment vessels. Randomisation implies an intention to treat the patient by the assigned procedure and the analysis of long term results will include all randomised cases. The trial will recruit at least 1000 patients who will be followed for five years. The major trial end points include death, new myocardial infarction, and new coronary angioplasty or coronary artery bypass procedures. Other outcome measures include symptom and employment status, quality of life, exercise tolerance, and left ventricular function.

For many patients with coronary artery disease percutaneous transluminal coronary angioplasty and coronary artery bypass surgery offer alternative methods of improving myocardial blood supply. The long term effects of coronary artery surgery have been assessed in three randomised clinical trials,[1-3] but information about the effects of coronary angioplasty is limited to registry studies.[4,5]

During 1986 and 1987 a small feasibility study examined the possibility of conducting a major randomised clinical trial to compare the effects of coronary angioplasty and coronary artery surgery. The feasibility study assessed whether patients and doctors would accept randomisation between such widely different treatments, and contributed to the development of a protocol for a large multicentre investigation. This protocol evolved into the Randomised Intervention Treatment of Angina (RITA) Trial, and a steering committee of interested and experienced cardiologists and surgeons was formed. Potential participating centres were invited to join the Randomised Intervention Treatment of Angina Trial and by November 1987 the trial protocol had been finalised. The Department of Health, the British Heart Foundation, and the British Cardiac Society agreed to support the Randomised Intervention Treatment of Angina Trial, and the first patient was randomised in March 1988. By July 1988 fourteen participating centres were entering patients into the trial.

Trial objectives and design

The Randomised Intervention Treatment of Angina Trial is a prospective, randomised, parallel group study to compare the short term and long term effects

---

Requests for reprints to Dr R A Henderson, Department of Cardiology, Guy's Hospital, St Thomas Street, London SE1 9RT.

*See Appendix.

Accepted for publication 20 June 1989

of percutaneous transluminal coronary angioplasty and coronary artery bypass surgery. Patients with arteriographically proven coronary artery disease are considered for the study if in the opinion of the participating cardiologist and cardiothoracic surgeon equivalent revascularisation could be achieved by either intervention procedure. All randomised patients will have detailed follow up for at least five years, and will be included in the analysis of long term results irrespective of the eventual treatment. The primary end points will be death, new myocardial infarction, and repeat coronary angioplasty or bypass surgery. An assessment will also be made of quality of life, exercise tolerance, and left ventricular function.

Coronary arteriogram register

To assess the relevance of the trial to clinical practice a register of all patients undergoing coronary arteriography at each participating centre is being maintained during the period of patient recruitment. The register is designed to encourage recruitment and to determine the reasons for excluding patients from the trial. The register is recording around 1000 patients per month and will provide independent information about the practice of coronary arteriography in the participating centres, which are sited throughout the United Kingdom.

Patient eligibility

Any patient, irrespective of sex or age, who has arteriographically proven coronary artery disease may be considered for the trial. Treatment by coronary angioplasty or coronary artery surgery must be considered necessary on clinical grounds, although it is not essential for patients to have angina if intervention is considered appropriate for reasons other than symptom relief. Patients with unstable angina, recent thrombolytic treatment, or poor left ventricular function may be included in the study as they form a large part of the routine workload of cardiac units. Patients with left main stem disease, previous coronary angioplasty or coronary bypass surgery, haemodynamically significant valve disease, or a systemic disease that will limit long term prognosis are all excluded from the study.

Patient selection

The coronary arteriograms of patients who may be eligible for the trial are reviewed by the participating cardiologist and cardiothoracic surgeon at each centre. The surgeon must be prepared to accept the patient for coronary artery surgery and the cardiologist must consider that the patient is suitable for coronary angioplasty. Before a patient can be randomised the investigators must jointly identify the major epicardial vessels that require treatment and must agree that equivalent revascularisation could be achieved by either treatment method. Thus the surgeon must prospectively state which vessels he intends to graft if the patient is randomised to surgery and the cardiologist must be prepared to attempt dilatation of all important stenoses in the same vessels. Coronary stenoses are regarded as important if there is a reduction in luminal diameter of at least 70% in one angiographic view or a 50% reduction in two views.

The trial does not require that all diseased vessels are treated, but the intention to achieve equivalent revascularisation by either treatment method may include totally occluded vessels. For instance, if a surgeon would graft the distal branches of a proximally occluded artery the cardiologist must be prepared to attempt to reopen the occlusion by coronary angioplasty. It is not necessary for angioplasty to be attempted in a vessel with subclinical lesions even if the surgeon would graft the vessel during a surgical procedure.

Stratification into groups with one, two, or three treatment vessels

Patients are prospectively stratified into groups with one, two, or three vessels requiring treatment; patients with more than three treatment vessels are ineligible for randomisation. All treatment vessels must be judged to supply 20% or more of the left ventricular myocardium and have at least one significant stenosis. A large side branch may qualify as a separate treatment vessel, but small diseased side branches are not separate treatment vessels even if they would be grafted or dilated.

Randomisation

Randomisation is carried out via a dedicated telephone line at the coronary care unit of the Royal Free Hospital, London. Patients are randomly assigned to treatment by coronary angioplasty or coronary bypass surgery, with prospective stratification by centre and by one, two, or three treatment vessels. The date of randomisation marks the patient's entry to the trial, and the assigned intervention procedure should be carried out as soon as possible.

Intervention procedure

Before joining the trial each participating centre was required to be performing substantial numbers of coronary angioplasty procedures, including multivessel dilatation, with a high success rate and low mortality. During the trial angioplasty and surgery will only be performed by fully trained operators. Because the trial will reflect contemporary cardiac practice no attempt has been made to standardise operative methods between centres.

In patients randomised to multivessel angioplasty some treatment vessels may not be successfully dilated at the first intervention procedure. Although the aim of intervention is to achieve equivalent revascularisation the decision to subject such patients to additional intervention procedures is to be based on clinical grounds.

Data collection

All data are recorded on specially prepared forms that are forwarded to the statistical centre and entered into a computerised data base. Baseline information recorded on all patients includes demographic data, cardiovascular risk factors, employment state, and physical activity level. Angina grade is assessed by the Canadian Cardiovascular Society Classification.[6] Quality of life is measured by the Nottingham Health Profile, which is a standardised questionnaire designed to measure an individual's perceived health.[7] Symptom limited exercise treadmill tests are performed according to the modified Bruce protocol,[8] unless the test is contraindicated because of unstable angina or intercurrent illness. Left ventricular function is assessed by gated radionuclide left ventriculography, and although the method may vary between centres radionuclide scans in individual patients will be repeated at the same centre by the same method. The pre-intervention coronary arteriogram findings are documented and the treatment vessels are prospectively identified.

During follow up patients are reviewed one, six, and twelve months after the intervention procedure and then two, three, four, and five years after the date of randomisation. In addition, patients are contacted every three months to confirm vital state and establish the occurrence of new cardiovascular events.

Trial events

The major events to be recorded during the trial include death, myocardial infarction, and new angioplasty or bypass graft procedures. All deaths and potential new myocardial infarcts will be independently assessed by a central review committee who are not aware of the patient's assigned treatment. Although the cause of death will be independently established in each case, the main comparative results will be analysed by mortality from all causes.

In addition to these major trial events a range of other outcome measures are recorded. At each follow up assessment, employment and symptom status and performance on an exercise treadmill are documented. The radionuclide ejection fraction is measured one and six months after intervention, and the Nottingham Health Profile is repeated six months after intervention and two years after randomisation. Other cardiovascular events occurring during follow up, including stroke and hospital admission for unstable angina, are also recorded. In order to evaluate the cost effectiveness of the different treatment policies the duration of all hospital admissions, including admissions to high dependency units, and the details of all repeat coronary arteriograms and repeat intervention procedures are documented.

Ethical considerations

The trial protocol has received ethical approval from the hospital ethics committees of all participating centres. The nature of the trial is explained in detail to all patients who are required to sign a standardised consent form before randomisation. Patients are at liberty to withdraw from the study at any time, although they are encouraged to decline randomisation unless they are prepared to proceed with the assigned intervention procedure.

Statistical considerations

It is intended that at least 1000 patients will be entered in the trial, the primary consideration being a reliable comparison of the rate of new myocardial infarction or death. If in five years there is a 20% incidence of this combined end point in one group, a trial of this size would have 80% power to detect a one third reduction in the incidence in the other group at the 5% significance level. Since the five year fatality rate will probably be lower than 20%, a trial of 1000 patients is likely to be too small to establish or refute that the treatments are equivalent for long term survival. However, 1000 patients will be sufficient to compare other end points such as symptoms, quality of life, exercise performance, and ejection fraction.

Trial organisation

The Randomised Intervention Treatment of Angina Trial comprises fourteen participating centres and a complex management structure including a steering committee of investigators, an executive committee, an ethics committee, and a statistical centre. The steering committee has overall responsibility for the conduct of the trial, but day to day management is supervised by the executive committee, which also monitors progress at each participating centre. The ethics committee is concerned with the welfare of the patients included in the trial, and is the only committee to which the comparative trial results will be available while the trial is in progress. The statistical centre is responsible for the randomisation of patients, and is maintaining the randomised trial data and the coronary arteriogram register. Each participating centre has employed a research assistant (usually an experienced nurse) to supervise the trial procedures and organise local data collection.

Conclusion

The protocol for the Randomised Intervention Treatment of Angina Trial has been described. The purpose of the study is to compare coronary angioplasty and coronary bypass surgery in suitable patients with coronary artery disease, and this can only reliably be achieved by a randomised clinical trial. Large multicentre clinical trials are difficult to conduct and require a multidisciplinary approach with cooperation across academic and clinical boundaries. Nevertheless, the Randomised Intervention Treatment of Angina Trial addresses an important issue and the results are likely to have major implications for the future management of patients with coronary artery disease. The results are also likely to influence allocation of resources for two expensive yet different methods of treatment.

The RITA Trial Steering Committee gratefully acknowledges additional financial support received from Advanced Cardiovascular Systems (USA), Medtronic (UK), and Schneider (UK).

Appendix

STEERING COMMITTEE OF INVESTIGATORS:
E Sowton (chairman), A K Yates (Guy's Hospital, London); C W Pumphrey, J R Pepper (St George's Hospital, London); P J B Hubner, R K Firmin (Groby Road Hospital, Leicester); R Balcon, P McGee (The London Chest Hospital, London); D C Cumberland, G H Smith (Northern General Hospital, Sheffield); K A A Fox, I M Breckenridge (University Hospital of Wales, Cardiff); N Brooks, H Moussalli (Wythenshawe Hospital, Manchester); S M Cobbe, D J Wheatley (Royal Infirmary, Glasgow); D S Dymond, S J Edmondson (St Bartholomews Hospital, London); D B O'Keefe, H O'Kane (Belfast City Hospital, Belfast); H C Miller, E W J Cameron (Royal Infirmary of Edinburgh, Edinburgh); M T Rothman, A J Wood (London Hospital, London); R H Swanton, T Treasure (Middlesex Hospital, London); D E Jewitt, J R W Keates (King's College Hospital, London)

EXECUTIVE COMMITTEE:
J R Hampton (chairman), E Sowton, S J Pocock, D G Julian, J Wallwork, R A Henderson

ETHICS COMMITTEE:
D A Chamberlain (chairman), M D Joy, J F Dark, S J Pocock

STATISTICAL CENTRE:
Clinical Trials Research Unit, Royal Free Hospital School of Medicine

References

1 The Veterans Administration coronary artery bypass surgery cooperative study group. Eleven-year survival in the Veterans Administration randomised trial of coronary bypass surgery for stable angina. *N Engl J Med* 1984;**311**:1333–9.

2 European Coronary Surgery Study Group. Long-term results of prospective randomised study of coronary artery bypass surgery in stable angina pectoris. *Lancet* 1982;**ii**:1173–80.

3 CASS principal investigators and their associates. Coronary artery surgery study (CASS): a randomised trial of coronary artery bypass surgery. Survival data. *Circulation* 1983;**68**:939–50.

4 Detre K, Holubkov R, Kelsey S, *et al.* Percutaneous transluminal coronary angioplasty in 1985–1986 and 1977–1981. The National Heart, Lung, and Blood Institute Registry. *N Engl J Med* 1988;**318**:265–70.

5 Kent KM, Bentivoglio LG, Block PC, *et al.* Long-term efficacy of percutaneous transluminal coronary angioplasty (PTCA): report from the National Heart, Lung, and Blood Institute PTCA Registry. *Am J Cardiol* 1984;**53**:27C–31C.

6 Cambeau L. Grading of angina pectoris. *Circulation* 1976;**54**:522–3.

7 Backett E, McEwen J, Hunt S. Report to the Social Science Research Council. *Health and quality of life.* 1981.

8 Sheffield LT. Graded exercise test (GXT) for ischaemic heart disease. A submaximal test to a target heart rate. In: *Exercise testing and training of apparently healthy individuals. A handbook for physicians.* Dallas: American Heart Association Committee on Exercise, 1972:35–8

Br Heart J 1989;**62**:415

Correspondence

Changes in transmitral velocities with heart rate

Sir,
During a study of changes in afterload induced by the cold pressor test, Smith *et al* (1989;**61**:344–7) recognised a relation between heart rate and transmitral velocities derived from pulsed Doppler recordings. We specifically studied the relation between transmitral velocities and differing RR intervals during exercise and respiration in healthy men.[1 2] We found a clear cut linear change in peak early transmitral velocity and late (active) transmitral velocity with increasing heart rate and decreasing RR interval. Early velocity increased on average by 16% when heart rate increased from 53 beats per minute to 94 beats per minute but active velocity increased by 89%. This led to a linear decrease in the ratio of peak early diastolic velocity to peak atrial velocity (E/A) (correlation coefficient $r = -0{\cdot}99$). Similarly, with respiratory induced sinus arrhythmia, the E/A ratio cycled in the opposite direction to the RR interval, so that as the heart rate increased the ratio fell.[2]

Doppler derived indices of left ventricular diastolic dysfunction that rely on transmitral velocities must take into account the relation with heart rate.

K S Channer,
Royal Hallamshire Hospital,
Glossop Road,
Sheffield S10 2JF.

J V Jones,
Bristol Royal Infirmary,
Bristol BS2 8HW.

References

1 Channer KS, Jones JV. The contribution of atrial systole to mitral diastolic blood flow increases during exercise in humans. *J Physiol* 1989;411:53–61.
2 Channer KS, Jones JV. Changes in the pattern of transmitral blood flow during respiration in man [Abstract]. *J Physiol* 1988;407:21p.

This letter was shown to the authors, who reply as follows:

Sir,
We thank Dr Channer and Dr Jones for their letter and support of our observations on the influence of heart rate on Doppler measurements of transmitral flow velocity.

When we examined the effect of a short term increase in blood pressure on transmitral velocities, we found that the duration of the RR interval profoundly influenced the peak atrial velocity (A or active) and its relation with early filling (A/E ratio). The studies of Channer and Jones during exercise and respiration further confirm this relation.[1 2]

Other circulatory variables such as preload that will be altered by exercise and respiration may also influence transmitral velocities. However, the studies of Channer and Jones suggest that nearly all of the change in A and A/E is due to changes in heart rate.[1 2] In several studies in which abnormal transmitral velocities were attributed to left ventricular diastolic dysfunction the effect of differences in heart rate were not taken into account.[3 4]

We agree that when transmitral velocities are used as indices of left ventricular diastolic function that heart rate must be controlled or taken into account.

P E Aylward,
A E Russell,
S A Smith,
J M Sheppard,
J E Stoner,
Flinders Medical Centre,
Bedford Park,
South Australia 5042.

References

1 Channer KS, Jones JV. Changes in the pattern of transmitral blood flow during respiration in man [Abstract]. *J Physiol* 1988;407:21P.
2 Channer KS, Jones JV. Change with exercise in the contribution of atrial systole to diastolic blood flow across the mitral valve in man [Abstract]. *J Physiol (Lond)* 1988;398:56P.
3 Zarich SW, Arbuckle BE, Cohen LR, Roberts M, Nesto RW. Diastolic abnormalities in young asymptomatic diabetic patients assessed by pulsed Doppler echocardiography. *J Am Coll Cardiol* 1988;**12**:114–20.
4 Phillips RA, Copland NL, Krakoff LR, *et al.* Doppler echocardiographic analysis of left ventricular filling in treated hypertensive patients. *J Am Coll Cardiol* 1987;**9**:317–22.

Br Heart J 1989;**62**:416

Notices

British Cardiac Society

The Annual General Meeting will take place in Torquay on 22 to 25 May 1990.

Vascular disease

The International Congress III: Lasers, Stents, and Interventions in Vascular Disease will take place in Scottsdale, Arizona on 11 to 16 February 1990. For further information contact Erika Scott, International Congress III, PO Box 10,000, Phoenix, AZ 85064, USA.

Cardiac ultrasound

The 5th International Postgraduate Course on Advances in Cardiac Ultrasound will be held in Davos, Switzerland on 26 to 30 March 1990. For further information write to Professor J R T C Roelandt, Thoraxcenter, Erasmus University, 3000 DR Rotterdam, The Netherlands.

Restenosis after coronary angioplasty

A one day international symposium on Restenosis after Coronary Angioplasty will be held in Leicester on 27 April 1990. Further details from Dr A H Gershlick, Department of Cardiology, Clinical Sciences Building, Glenfield General Hospital, Groby Road, Leicester LE3 9QP.

Echocardiography and Doppler in cardiac surgery

The Third International Symposium on Echocardiography and Doppler in Cardiac Surgery will take place in Vienna on 9 to 12 May 1990. For further information write to Interconvention, A-1450 Vienna, Austria.

Pacing and electrophysiology

The 11th Annual Scientific Session of the North American Society of Pacing and Electrophysiology will be held in San Diego, California on 31 May to 2 June 1990. For further information contact NASPE, 13 Eaton Court, Wellesley Hills, MA 02181, USA.

Ultrasound angiography

An international conference on Ultrasound Angiography will be held at the University of London on 25 to 28 September 1990. Further details from The Conference Secretariat, PO Box 15, Eastleigh, Hampshire SO5 5XG.

December 1989 Vol 62 No 6

vcm (books)

British Heart Journal

A monthly journal of cardiology published in association with the British Cardiac Society

Integration of ambulance staff trained in cardiopulmonary resuscitation with a medical team providing prehospital coronary care *W A McCrea, E Hunter, C Wilson* **417**

Haemorrheological abnormalities in unstable angina pectoris: a relation independent of risk factor profile and angiographic severity *F-J Neumann, H Tillmanns, P Roebruck, R Zimmermann, H-M Haupt, W Kübler* **421**

Estimation of the risk of death during the first year after acute myocardial infarction from systolic time intervals during the first week *B J Northover* **429**

A comparison of methods of analysing exercise tests for diagnosis of coronary artery disease *J W Deckers, B J Rensing, J G P Tijssen, R V H Vinke, A J Azar, M L Simoons* **438**

Physiological hypertrophy of the heart and atrial natriuretic peptide during rest and exercise *J Svanegaard, K Angelo-Nielsen, J S Hansen* **445**

Clinical course of endomyocardial fibrosis *P N Gupta, M S Valiathan, K G Balakrishnan, C C Kartha, M K Ghosh* **450**

Right ventricular function 10 years after the Mustard operation for transposition of the great arteries: analysis of size, shape, and wall motion *A N Redington, M L Rigby, P Oldershaw, D G Gibson, E A Shinebourne* **455**

Cardiac involvement in Churg-Strauss syndrome shown by echocardiography *J M Morgan, L Raposo, D G Gibson* **462**

Case reports

Potential value of intraoperative Doppler colour flow mapping in operations for complex intracardiac shunting *G R Sutherland, S Balaji, J L Monro* **467**

Unusual and intraoperative epicardial echocardiographic features of a papillary tumour of the aortic valve *N P Lewis, G T Williams, A G Fraser* **470**

Severe haemolytic anaemia after replacement of the mitral valve by a St Jude medical prosthesis *H Feld, J Roth* **475**

Hypoplastic right retro-oesophageal aortic arch: similarities to interrupted aortic arch *W B Knight* **477**

British cardiology

Staffing in cardiology in the United Kingdom 1988: Fifth biennial survey *D Chamberlain, L Bailey, E Sowton, D Ballantyne, D McC Boyle, M Oliver* **482**

Book review **488**

Correspondence **489**

Notices **492**

Index **493**

British Medical Association

ASTM CODEN: BHJUAV 62(6) 417–501 (1989)
ISSN 0007-0769

British Heart Journal

EDITOR Dennis Krikler ASSISTANT EDITORS M J Davies, Kim Fox, Peter Mills

EDITORIAL COMMITTEE
Clive P Aber Kate Bull Keith Dawkins Alan B Houston Barry R Keeton Michael Marmot
Alexander L Muir Paul J Oldershaw Philip A Poole-Wilson David B Shaw
Tom Treasure David E Ward John Watkins Peter Wilde
Editor: *British Medical Journal* Editor: *Cardiovascular Research*

TECHNICAL EDITOR Jane Dawson EDITORIAL ASSISTANT Anne Oliver
STATISTICAL ADVISER Stephen J W Evans

Notice to contributors

Papers relating to the heart and circulation should be sent in triplicate to the Editor, British Heart Journal, BMA House, Tavistock Square, London WC1H 9JR, and be prepared according to the *Uniform requirements for manuscripts submitted to biomedical journals* (Vancouver agreement) (*Br Med J* 1988;**296**:401–5). Authors are asked to complete a copy of the checklist provided (1989;**61**:131–2 (January issue)) when submitting their manuscripts for publication. The reference number given on the acknowledgement postcard sent out by the editorial office should be quoted on all subsequent correspondence and telephone inquiries. A covering letter must be signed by all authors stating that they have seen and approved the paper and that the work has not been, and will not be, published elsewhere. All authors will be required to transfer copyright of their articles to the journal before publication. (All material for possible publication (including Letters to the Editor) *must* be typed in *double spacing* with 4 cm margins.)

Ethical standards

Authors are expected to comply with the code of ethics known as the Declaration of Helsinki. Where appropriate, manuscripts should include a statement that the research protocol has been approved by the locally appointed ethics committee and that the informed consent of the subjects has been obtained.

Case reports should convey only the essential facts of a case and the discussion and bibliography be kept to a minimum. They should have no more than three authors, should not exceed 1500 words, and include no more than two Figures.

Abbreviations should *not* be used in the text, except for mathematical calculations and units of measurement.

References must be cited precisely according to the Vancouver agreement and be typed in *double spacing*. As a general rule, no more than three references should be cited for any one statement.

Authors are responsible for the accuracy of any references cited: these should be checked at source or with the listing in Index Medicus.

Units of measurement

All haematological and clinical chemistry measurements should be given as SI units. Blood pressures should be given in mm Hg. Measurements of length, height, weight, and volume should be reported in metric units and temperatures should be reported in degrees Celsius.

Tables must be typed on separate sheets and not in the text. Titles should be provided, and all abbreviations used must be given in full in a footnote.

Illustrations (for general requirements, please refer to *Br Heart J* 1984; **51:** 1–6).

Electrocardiograms: Black and white prints only should be sent and not the original tracings. If several tracings are grouped in a single Figure only a few complexes should be shown; the width should not exceed 14 cm unless a reduction in scale is possible.

Echocardiograms: Since these will be reproduced at a width of 7 cm or less all unnecessary or irrelevant detail (such as electronic writing) should be removed. Labelling must be superimposed directly on to the print itself and only where essential be shown on an accessory drawing. Echocardiograms obtained with 30° sector scans or bistable equipment or recorded on ultraviolet paper are not suitable for publication.

Figure legends must include an explanation of all abbreviations used in the Figure.

Copyright permission to reproduce material published elsewhere must be obtained in writing and acknowledged in the manuscript.

Proofs of articles accepted for publication will be sent for the author's approval. Proof corrections should be kept to a minimum.

Notice to subscribers

British Heart Journal is published monthly. The annual subscription rates are £106.00 inland and £124.00 overseas (USA $200·00). Combined rate: *British Heart Journal* and *Cardiovascular Research* £200 inland and £233 overseas (USA $385·00). Orders should be sent to The Subscription Manager, *British Heart Journal*, BMA House, Tavistock Square, London WC1H 9JR. Orders can also be placed with any leading subscription agent or bookseller. Subscribers may pay for their subscriptions by Access, Visa, or American Express by quoting on their order the credit or charge card preferred together with the appropriate personal account number and the expiry date of the card. (For the convenience of readers in the USA subscription orders ($200) with or without payment may also be sent to British Medical Journal, Box 560B, Kennebunkport, Maine 04046. All inquiries, however, must be addressed to the Publisher in London.) **All copies are despatched by air-speed.** First class rates available on request.

COPYRIGHT © 1989 by the *British Heart Journal*. All rights reserved. No part of this publication may be reproduced, stored in a retrieval system, or transmitted in any form or by any means, electronic, mechanical, photocopying, recording, or otherwise, without the prior permission of the *British Heart Journal*.

Second class postage paid, Rahway NJ Postmaster: send address changes to: British Heart Journal c/o Mercury Airfreight International Ltd Inc, 2323 Randolph Avenue, Avenel, NJ 07001, USA.

Br Heart J 1989;62:417–20

Integration of ambulance staff trained in cardiopulmonary resuscitation with a medical team providing prehospital coronary care

W A McCREA, E HUNTER, C WILSON

From Waveney Hospital, Ballymena, Northern Ireland

SUMMARY Ambulance staff with advanced training in cardiopulmonary resuscitation and equipped with monitor/defibrillators were used as the initial responders to collapse calls within a medically based prehospital coronary care system. During 21 months, in a population of approximately 120 000, ambulance staff successfully resuscitated six patients from ventricular fibrillation; there were four long term survivors. The median response time of emergency ambulances to collapse calls was eight minutes compared with 20 minutes for the medically manned mobile coronary care unit. None of the patients resuscitated by ambulance staff would have survived if they had been dependent on the mobile coronary care unit acting alone. Nineteen other patients with important arrhythmias were referred for earlier medical management which in some cases may have saved lives. An additional eight long term survivors of out of hospital ventricular fibrillation were resuscitated by medical staff.

The integration of paramedical with medical prehospital coronary care improved survival after out of hospital cardiac arrest.

The beneficial effect of a medically manned mobile coronary care unit on community mortality from myocardial infarction in the Antrim and Ballymena district has already been reported.[1] In addition, the results of equipping general practitioners in this district with portable defibrillators have been encouraging.[2 3] However, cardiac arrest, often without warning symptoms, may occur when medical attention is not immediately available. Survival is critically dependent on prompt cardiopulmonary resuscitation and delivery of definitive care, in particular defibrillation.[4-6] The efficacy of a medically manned mobile unit in out of hospital cardiac arrest is limited by its operation from a single despatch centre and by the inevitable delay while the doctor and nurse are collected. Although general practitioners are usually closer to the patient they may not be immediately available or a bystander may initially telephone 999 for an emergency ambulance.

There are obvious advantages in using emergency ambulance staff when a delay of a few minutes may be critical. In this district an ambulance can be despatched from either of two stations situated 13 miles apart or diverted from a less urgent call if it is in the vicinity of a collapsed patient.

Ambulance staff trained in defibrillation techniques can successfully resuscitate patients from cardiac arrest outside hospital.[7] However, the limited capability of paramedical workers to stabilise the patient's haemodynamic state with appropriate drug treatment after successful defibrillation may contribute to the low long term survival rates in this group.[7-9] Some predict that more complete stabilisation by a skilled medical team after defibrillation and before transfer to hospital would improve the outcome.[10]

We decided to train emergency ambulance staff to provide initial definitive resuscitation in patients with cardiac collapse and to back up this team with prompt support from the medical team on a mobile coronary care unit.

Patients and methods

Since 1966 the Antrim and Ballymena district, population 120 000, has been served by a medically staffed mobile coronary care unit operating from the Waveney Hospital coronary care unit,[11] and in 1982 general practitioners were provided with

Requests for reprints to Dr C Wilson, Waveney Hospital, Ballymena BT43 6HL, Northern Ireland.

Accepted for publication 28 July 1989

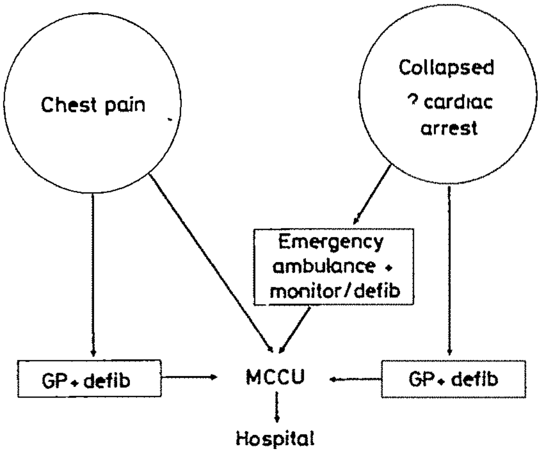

Chest pain
Collapsed ? cardiac arrest
Emergency ambulance + monitor/defib
GP + defib
MCCU
GP + defib
Hospital

Fig 1 *Ballymena prehospital coronary care system. GP, general practitioner; MCCU, mobile coronary care unit (medically staffed).*

defibrillators. In July 1986 we initiated a voluntary two week cardiac training programme for ambulance staff. Volunteers were taken in groups of four. During the first week they had five 75 minute tutorials in basic cardiac anatomy and physiology, myocardial infarction, electrocardiographic interpretation of cardiac rhythm and arrhythmias, and the use of a Hewlett-Packard monitor/defibrillator type 43120A. They practised resuscitation and defibrillation techniques on a training mannequin with cardiac arrhythmia simulator (Laerdal Arrhythmia Anne IV). Subsequently the pairs of trainees spent a week on the coronary care unit watching the emergency management of myocardial infarction, with emphasis on electrocardiographic monitoring and arrhythmia recognition. They were encouraged to use a defibrillator when the opportunity arose. They were also taught to measure systolic blood pressure by radial pulse palpation with an aneroid sphygmomanometer.

When they arrived at a collapsed patient they were advised to define the cardiac rhythm as quickly as possible. If ventricular fibrillation was present, defibrillation was applied immediately and the mobile coronary care unit was summoned. An initial direct current shock of 200 J was delivered followed if necessary by further shocks of 360 J. Additional resuscitative measures were continued as required until medical support arrived. If the initial rhythm was agonal with electromechanical dissociation or asystole, resuscitation was not attempted; a rhythm strip was recorded for documentation and the mobile coronary care unit was not activated. Other arrhythmias were observed, recorded, and assessed and if a coronary event was suspected the mobile unit was summoned. The systolic blood pressure was recorded when possible and oxygen with or without nitrous oxide was administered if chest pain or dyspnoea was present.

On completion of the training course each trainee underwent an oral and practical examination by a panel comprising the authors and a second senior ambulance officer. A high level of accuracy and expertise was demanded and by 1 October 1986, 18 out of 20 volunteers from a total of 28 emergency ambulance personnel employed in the district achieved the required standard. All seven emergency ambulances were then equipped with Hewlett-Packard 43120A monitor/defibrillator units and the duty rosters were arranged so that at least one person in the crew of two had been trained in cardiopulmonary resuscitation. Every two months trained staff attended a one hour refresher course.

We have now a comprehensive system for prehospital coronary care (fig 1). People with chest pain usually summon their general practitioners but, if they are not available the mobile coronary care unit may be requested directly via the 999 system. In the event of a patient's sudden collapse the general practitioner may be able to attend promptly, or alternatively a 999 call alerts the nearest emergency ambulance. When necessary the mobile coronary care unit attends as quickly as possible to stabilise the patient's cardiac rhythm and haemodynamic state before transfer to hospital.

Results

During the first 21 months of this scheme 116 patients with cardiac arrest were attended by the emergency ambulance crews (table 1). In 43 patients the cardiac rhythm was not recorded because they were obviously beyond resuscitation and these individuals were classified as dead on arrival. Ventricular fibrillation was the initial documented rhythm in 18 patients of whom six (33%) had received bystander cardiopulmonary resuscitation compared with 13 (24%) of the 55 in whom there was asystole or agonal rhythm. Defibrillation was attempted in all patients with ventricular fibrillation; when the mobile coronary care unit arrived six had a

Table 1 *Cardiac arrests attended by emergency ambulance staff*

Dead—rhythm not documented	43
Asystole	29
Agonal rhythm	26
Ventricular fibrillation:	18
Survived to medical care	6
Discharged alive	4

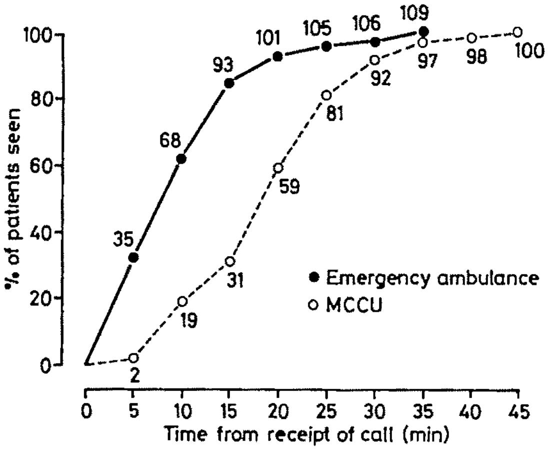


Fig 2 *Response of emergency ambulances to 109 patients with cardiac arrest (response times not recorded for seven patients) compared with the response of the medically staffed mobile coronary care unit (MCCU) to 100 consecutive cardiac emergencies. The number of patients is shown.*

cardiac output—four of them were in sinus rhythm, one had atrial fibrillation, and one had nodal rhythm. One patient died of cardiogenic shock before transfer to hospital and another, who had an acute anterior myocardial infarction, died from cardiac rupture three days after admission to hospital. Of the four patients who survived to discharge two men, aged 40 and 57, had acute transmural myocardial infarction and two, a 66 year old man and a 73 year old woman, had neither electrocardiographic nor biochemical evidence of acute myocardial necrosis but both had previous infarction. None of the survivors had appreciable persistent cerebral impairment.

The median response time from receipt of a collapse call to the arrival of the emergency ambulance at the scene was eight minutes compared with the mobile coronary care unit's median response time of 20 minutes for 100 consecutive calls documented during this study (fig 2). For the 18 cases of ventricular fibrillation the mean response time for the emergency ambulance was eight (range 1–16) minutes while the mean response time for the mobile coronary care unit to these patients after they were summoned by the emergency ambulance was 18 (range 6–30) minutes. An additional 78 arrhythmias were documented by the emergency ambulance crews in patients without cardiac arrest (table 2). As a result, at least 19 people with haemodynamically important or possibly life threatening arrhythmias (ventricular tachycardia, R on T ventricular extrasystoles, supraventricular tachycardia, and complete heart block) received appropriate therapeutic intervention earlier.

Table 2 *Arrhythmias documented by ambulance staff in patients without cardiac arrest*

Ventricular tachycardia	3
R on T ventricular extrasystoles	5
Supraventricular tachycardia	8
Complete heart block	3
Atrial fibrillation	19
Sinus bradycardia	14
Benign ventricular extra systoles	25
First degree heart block	1

During this study, 21 of those patients who presented with cardiac pain and who were initially attended in the usual way by general practitioners and/or the medically manned mobile coronary care unit developed ventricular fibrillation outside hospital and were defibrillated by general practitioners (six patients) or by the mobile unit team (15 patients). Eight of these 21 patients survived to reach hospital and all eight were discharged alive.

Therefore, within our overall prehospital coronary care scheme, 39 patients were treated for out of hospital ventricular fibrillation, 13 (33%) survived to reach hospital and 12 (31%) were discharged alive.

Discussion

This study shows the benefit of using ambulance staff trained in cardiopulmonary resuscitation in addition to established medically based prehospital coronary care. The response times of the emergency ambulances and the mobile coronary care unit show that the patients resuscitated from ventricular fibrillation by emergency ambulance crews would not have survived if they had been dependent on the mobile coronary care unit acting alone. The greater success rate achieved by general practitioners and the mobile coronary care unit reflects the fact that most of these cardiac arrests occurred in their presence so that defibrillation could usually be applied immediately, while all patients defibrillated by emergency ambulance crews had been in ventricular fibrillation for several minutes. The high recorded incidence of asystole and agonal rhythm also reflects the length of time that had elapsed from the onset of cardiac arrest in many patients, because ventricular fibrillation rapidly deteriorates to these terminal rhythms if no action is taken. The ability of the ambulance crews to recognise arrhythmias other than those associated with cardiac arrest resulted in earlier referral of many patients for possibly life saving medical treatment.

In view of the catchment population the results achieved by our prehospital coronary care scheme compare favourably with those reported elsewhere.[8,9,12] Prehospital coronary care schemes dependent on paramedical staff acting alone reported survival rates of 36% to 63% for patients admitted after out of hospital resuscitation.[9,12,13] Our high survival rate for patients admitted to the coronary care unit after out of hospital resuscitation (12 of 13) indicates the benefits of prompt stabilisation of the patient's condition by a skilled medical team before transfer to hospital.

The two week training course for the ambulance staff is similar to those described by Rowley *et al*[14] and Jakobsson *et al.*[15] When skilled medical support is rapidly available training ambulance staff in the administration of parenteral drugs and intubation would yield only marginal, if any, benefit and would increase the cost of the programme by prolonging the training period.

In Seattle it has been found that after a few years the percentage of patients resuscitated from ventricular fibrillation outside hospital tends to plateau, mainly because of the delay in initiating basic life support and defibrillation.[6] A community training programme in cardiopulmonary resuscitation improves the efficacy of prehospital coronary care.[6,16] In this study those patients whose initial documented rhythm was ventricular fibrillation were more likely to have received cardiopulmonary resuscitation initiated by a bystander than those whose rhythm was asystolic or agonal, which suggests that bystander cardiopulmonary resuscitation may have maintained some individuals in a condition amenable to resuscitation. However, only 17% of our cardiac arrest victims received cardiopulmonary resuscitation from bystanders compared with 40% in Seattle where at least 370 000 citizens have taken part in a community training programme.[6] Because cardiopulmonary resuscitation training is time consuming and at least half of the victims of out of hospital cardiac arrest have known coronary heart disease,[17,18] it may be more rewarding to target relatives of cardiac patients for training. Consequently we now offer training in basic life support to relatives of our cardiac inpatients and we expect this policy to yield increasing dividends in the future.

We thank the staff on the emergency ambulances and ambulance controllers for their willing co-operation, enthusiasm, and dedication, also the coronary care unit nursing staff and physiologicl measurement technicians for their invaluable help in the training programme.

Financial support for a research grant and equipment was provided by the Waveney Hospital cardiac fund and the Department of Community Medicine, Northern Health and Social Services Board.

References

1 Mathewson ZM, McCloskey BG, Evans AE, Russell CJ, Wilson C. Mobile coronary care and community mortality from myocardial infarction. *Lancet* 1985; i:441–4.

2 Clyde C, Kerr A, Varghese A, Wilson C. Defibrillators in general practice. *Br Med J* 1984;**289**:1351–3.

3 Varghese A, Wilson C. Successful defibrillation by general practitioners related to distance from hospital. *Cardiovascular Reviews and Reports* 1986;7:527–37.

4 Ritter G, Wolfe RA, Goldstein S, *et al.* The effect of bystander CPR on survival of out-of-hospital cardiac arrest victims. *Am Heart J* 1985;**110**:932–7.

5 Weaver WD, Cobb LA, Hallstrom AP, Fahrenbruch C, Copass MK, Ray R. Factors influencing survival after out-of-hospital cardiac arrest. *J Am Coll Cardiol* 1986;7:752–7.

6 Weaver WD, Cobb LA, Hallstrom AP, *et al.* Considerations for improving survival from out-of-hospital cardiac arrest. *Ann Emerg Med* 1986;15:1181–6.

7 Briggs RS, Brown PM, Crabb ME, *et al.* The Brighton resuscitation ambulances: a continuing experiment in prehospital care by ambulance staff. *Br Med J* 1976; 2:1161–5.

8 Jakobsson J, Nyquist O, Rehnqvist N. Effects of early defibrillation of out-of-hospital cardiac arrest patients by ambulance personnel. *Eur Heart J* 1987;**8**:1189–94.

9 Rowley JM, Mounser P, Garner C, Hampton JR Advanced training for ambulance crews: implications from 403 consecutive patients with cardiac arrest managed by crews with simple training. *Br Med J* 1987;**295**:1387–9.

10 Adgey AAJ, Geddes JS, Webb SW, *et al.* Acute phase of myocardial infarction. *Lancet* 1971;**ii**:501–4.

11 Kernohan RJ, McGucken RB. Mobile intensive care in myocardial infarction. *Br Med J* 1968;**iii**:178–80.

12 Mackintosh AF, Crabbe ME, Grainger R, Williams JH, Chamberlain DA. The Brighton resuscitation ambulances: review of 40 consecutive survivors of out-of-hospital cardiac arrest. *Br Med J* 1978;**i**: 1115–8.

13 Eisenberg MS, Hallstrom AP, Copass MK, Bergner L, Short F, Pierce J. Treatment of ventricular fibrillation. *JAMA* 1984;**251**:1723–6.

14 Rowley JM, Garner C, Handy M, Hampton JR. Simple training programme for ambulance personnel in the management of cardiac arrest in the community. *Br Med J* 1985;**291**:1099–101.

15 Jakobsson J, Nyquist D, Rehnqvist N. Concise education of ambulance personnel in ECG interpretation and out-of-hospital defibrillation. *Eur Heart J* 1987; 8:229–33.

16 Cobb LA, Hallstrom AP. Community-based cardiopulmonary resuscitation: what have we learned? *Ann NY Acad Sci* 1982;**382**.330–42.

17 Liberthson RR, Nagel EL, Hirschman JC, Nussenfield SR, Blackbourne BD, Davis JH. Pathophysiologic observations in prehospital ventricular fibrillation and sudden cardiac death. *Circulation* 1974;**49**:790–8.

18 Baum RS, Alvarez H, Cobb LA. Survival after resuscitation from out-of-hospital ventricular fibrillation. *Circulation* 1974;**50**:1231–5.

Br Heart J 1989;62:421–8

Haemorrheological abnormalities in unstable angina pectoris: a relation independent of risk factor profile and angiographic severity

FRANZ-JOSEF NEUMANN, HARALD TILLMANNS, PETER ROEBRUCK,* RAINER ZIMMERMANN, HEIDE-MARLEN HAUPT, WOLFGANG KÜBLER

*From the Medizinische Universitätsklinik III (Kardiologie), *Institut für medizinische Biometrie und Informatik, Ruprecht-Karls Universitat Heidelberg, Heidelberg, Federal Republic of Germany*

SUMMARY Plasma viscosity, photometric erythrocyte aggregation index, and erythrocyte filterability were measured in 194 patients with coronary artery disease. Patients with unstable angina ($n = 64$) had a higher plasma viscosity and photometric erythrocyte aggregation index than patients with stable angina (95% confidence intervals for the mean difference: 0·052–0·100 mPa·s for plasma viscosity, and 43%–72% for the photometric erythrocyte aggregation index). Multiple regression with fibrinogen, cholesterol, high density lipoprotein cholesterol, triglycerides, blood pressure, smoking habits, coronary artery score, and left ventricular ejection fraction as independent variables showed a significant partial correlation between fibrinogen and the photometric erythrocyte aggregation index ($r^2 = 0{\cdot}20$) and plasma viscosity ($r^2 = 0{\cdot}09$), between triglycerides and plasma viscosity ($r^2 = 0{\cdot}05$), and between aortic pressure and erythrocyte filterability ($r^2 = 0{\cdot}03$). Logistic regression for unstable/stable angina with the haemorrheological variables as independent variables correctly identified 72% of the patients with stable angina and 78% of those with unstable angina. Inclusion of all the variables investigated did not substantially improve the discriminative potential of the logistic regression model.

Unstable angina is associated with an impairment of blood fluidity that is essentially independent of risk factor profile and angiographic data.

There is still uncertainty on the implications of blood fluidity for symptoms and prognosis in ischaemic heart disease. Experimental data indicate that the physical properties of blood are major determinants of blood flow in the capillaries[1–4] and of oxygen transport.[5] The severity and extent of myocardial ischaemia produced by a given degree of coronary artery stenosis can be modified by haemorrheological alterations. Various studies have been designed to detect haemorrheological abnormalities in chronic coronary artery disease[6–9] and in acute myocardial infarction.[10 11] The abnormalities described, however, may be secondary phenomena. In acute myocardial infarction, the haemorrheological abnormalities can be explained by the acute phase response induced by necrosis.[12 13] In chronic coronary artery disease the haemorrheological alterations can be attributed to changes in risk factor profile[14–18] or in the extent of coronary atherosclerosis.[6]

We investigated whether there is a relation between unstable angina pectoris and haemorrheological abnormalities in chronic coronary artery disease that is independent of the extent of coronary atherosclerosis, left ventricular function, and risk factor profile.

Patients and methods

PATIENT SELECTION

Patients undergoing coronary angiography for suspected coronary artery disease were eligible for the study. Exclusion criteria were: (*a*) interfering noncardiac diseases—that is, anaemia, infection, carcinoma, collagen diseases, diabetes mellitus, thyrotoxicosis; (*b*) cardiac diseases other than coronary artery disease (for example dilated or hypertrophic cardiomyopathy and valvar heart disease, except for

Requests for reprints to Dr Franz-Josef Neumann, Medizinische Universitätsklinik III, Bergheimerstrasse 58, 6900 Heidelberg, Federal Republic of Germany.

Accepted for publication 10 August 1989

minor mitral regurgitation); (*c*) overt right or left ventricular failure; (*d*) absence of significant coronary artery disease—that is lack of stenoses causing $\geq$ 50% narrowing in luminal diameter; (*e*) previous coronary artery bypass surgery or percutaneous transluminal coronary angioplasty; (*f*) myocardial infarction within the three months preceding the study; (*g*) myocardial infarction evolving within 8 hours after withdrawal of blood for haemorrheological investigation. All patients in whom serum concentrations of creatine kinase increased with a concomitant rise in the concentration of the MB isoenzyme were assumed to have evolving myocardial infarction. Furthermore, patients with ST segment elevation of $> 0\cdot1$ mV in at least one lead lasting for > 30 minutes as well as those with intractable angina were excluded from the study because of suspected myocardial infarction. According to these criteria, 197 consecutive patients were included in the study. Three of them were subsequently excluded because of evolving myocardial infarction.

The study population was subdivided into two groups: patients with stable angina (group 1) and those with unstable angina (group 2). Unstable angina was defined by the presence of at least one of the following features: (*a*) angina of recent onset—that is within six weeks or less, brought on by minimal exertion; (*b*) crescendo angina—that is more severe, prolonged, or more frequent anginal attacks, superimposed on chronic effort angina; (*c*) angina at rest lasting for at least 15 minutes.

The study protocol did not affect the medical treatment of the patients or early intervention in patients with unstable angina. The study was approved by the local ethics committee.

The control group consisted of 50 healthy volunteers (42 men and eight women, mean (SD) age 49·1 (5·8) years).

RISK FACTOR PROFILE

The risk factor profile was determined at entry into the study. Blood pressure was taken as the mean from three measurements (Riva-Rocci) on admission to hospital, according to the formula: mean blood pressure = (systolic blood pressure + 2 × diastolic blood pressure)/3. Serum lipid concentrations were measured after a 12 hour overnight fast. Serum triglycerides and cholesterol were assayed enzymatically (Boehringer Mannheim, Mannheim, Federal Republic of Germany, triglyceride kit No 297771, cholesterol kit No 237574). High density lipoprotein cholesterol was determined after ultracentrifugation and microprecipitation.[19] Patients were classified as smokers, ex-smokers, and non-smokers. Ex-smokers included all patients who had given up smoking for more than 42 days and less than five years. Patients who had given up smoking for more than five years were regarded as non-smokers.

ANGIOGRAPHIC EVALUATION

Coronary angiography was performed by the Judkins technique.[20] Multiple views, including angulated views, were obtained of both coronary arteries. The angiograms were reviewed independently by two experienced cardiologists who were unaware of the haemorrheological results. The luminal reduction was visually estimated on the angiographic view showing the most severe stenosis. All stenoses with an estimated luminal reduction of at least 25% were scored, except for those in hypoplastic segments or those in segments distal to total occlusions or severe stenoses in which contrast filling was inadequate. The score for each lesion was based on the estimated luminal reduction as follows: < 25–50%; < 50–75%; < 75–90%; lumen almost totally obliterated but still showing anterograde flow; total occlusion. The total coronary score was obtained by taking the sum of the scores of each lesion. For calculation of left ventricular ejection fraction, end diastolic volume and end systolic volume were derived from left ventricular cineangiogram in the 30° right anterior oblique view. Both ventricular volumes were determined from a beat in one of the four normal cardiac cycles after a normally conducted beat.

HAEMORRHEOLOGICAL ANALYSIS

Blood for haemorrheological investigations was taken from the antecubital vein without a tourniquet. Edetic acid was used as anticoagulant. All samples were obtained in the morning before coronary angiography. The haematocrit was determined by the microhaematocrit method (13 000 × *g* for 5 minutes), and plasma viscosity by capillary viscometry (Coulter-Harkness viscometer[21]). Erythrocyte aggregation was analysed photometrically at an adjusted haematocrit of 35 (1) % with the mini-aggregometer (Myrenne, Roetgen, Federal Republic of Germany).[22 23] The integral of the photovoltage curve in stasis for the first ten seconds after mixing was taken as a measure of erythrocyte aggregation. The readings were normalised to the mean value of the control group to obtain the photometric erythrocyte aggregation index. Erythrocyte deformability was determined by a filtration method[24 25] (MF4-Filtrometer, Myrenne, Roetgen, Federal Republic of Germany). Calibrated metal microsieves with pores of 4·3 μm in diameter and 12 μm in length were used (Myrenne, Roetgen). After removal of the buffy coat, erythrocytes were suspended in buffer (sodium chloride 137 mmol/l, potassium chloride 4 mmol/l, calcium chloride 1·8 mmol/l, sodium phosphate 0·8 mmol/l, sodium acid phosphate 0·2 mmol/l, magnesium sulphate 0·7 mmol/l, glucose 5·5 mmol/l, HEPES 8·4 mmol/l, human albumin 1 g/l). Residual leucocytes were removed by filtering the suspension through Imugard wool (Terumo, Tokyo, Japan). In all instances, leucocyte counts were $< 15/\mu l$. The haematocrit of the suspension was adjusted to 8%. Erythrocyte deformability was measured (in relation to buffer alone) as passage through the microsieve of the erythrocyte suspension at 200 Pa filtration pressure.[25] Plasma concentrations of fibrinogen were measured by the method of Clauss.[26]

STATISTICAL ANALYSIS

If not indicated otherwise results are expressed as mean (SD). For the comparison of two groups, continuous variables were tested by the Mann-Whitney-Wilcoxon rank sum test, and the 95% confidence intervals for differences between means were calculated assuming a normal distribution. Frequencies were compared by the χ^2 test.

The possible influence of risk factor profile and angiographic findings on haemorrheological variables was analysed by multiple linear regression. (Smoking habits were coded as 1 for non-smokers, 2 for ex-smokers, and 3 for smokers). The multiple coefficient of determination resulting from least squares estimation of the models is the part of the variability of the respective dependent variable (haemorrheological variable) that is attributable to the independent variables in the model. The contributions of single factors to the model were judged by significance tests of the respective regression coefficients.

The diagnostic value of several sets of variables for stable/unstable angina was analysed by logistic regression, which models the probability p of unstable angina as $\ln(p/(1-p)) = \Sigma\, \beta_i x_i$. The x_i are the independent predictor variables of the model (including a constant term), and the respective coefficients β_i are estimated from the data by maximum likelihood methods. Predictor variables were eliminated by stepwise variable selection if their influence was negligible in relation to the other variables. We used the estimated models to measure the probability of unstable angina for each individual member of the sample ($\hat{p}$). Patients were reclassified as having stable or unstable angina, depending on whether $\hat{p}$ was greater or smaller than some suitable chosen cut off point. The proportion of correctly reclassified patients is a measure of the diagnostic reliability of the predictor variables (slightly overestimated).

Both types of analysis could only be performed when a complete set of variables was known for each patient; thus some cases with missing values were omitted. Values for left ventricular ejection fraction were missing in 36 cases (because of frequent extrasystoles during cineangiography), for high density lipoprotein cholesterol in seven patients, and for fasting concentrations of all lipids in 14 patients.

Results

CHARACTERISTICS OF THE STUDY POPULATION

Table 1 compares the clinical characteristics of patients with stable angina (group 1) with those of patients with unstable angina (group 2). There were no significant differences between both groups in terms of age, sex distribution, smoking habits, arterial blood pressure, serum concentrations of triglyceride, and left ventricular ejection fraction. However, the mean coronary score was significantly higher in group 2 than in group 1; and more patients in group 2 had more vessels affected. Likewise, serum cholesterol levels were significantly higher and serum concentrations of high density lipoprotein cholesterol were significantly lower in group 2 than in group 1. Drug treatment in the two study groups differed considerably (table 2). In group 2 a larger proportion of patients was treated with β blocking agents and nitrates than in group 1. Furthermore, most of the patients with unstable angina were taking aspirin, while most of the patients with stable angina were not taking antiplatelet drugs.

HAEMORRHEOLOGICAL DATA (FIG 1)

Plasma viscosity ($p < 0\cdot001$) (fig 1 b), photometric

Table 1 *Characteristics (mean (SD)) of the study population*

Variable	*Group 1 (n = 130)*	*Group 2 (n = 64)*	*Significance*
Age	54·6 (7·6)	52·7 (6·9)	NS
Males	n = 108 (82%)	n = 52 (81%)	NS
Systolic BP (mm Hg)	134 (18)	129 (16)	NS
Diastolic BP (mm Hg)	84 (12)	83 (11)	NS
Triglycerides (mg/dl)	207 (141)	212 (153)	NS
Cholesterol (mg/dl)	240 (50)	259 (58)	p < 0·05
HDL-cholesterol (mg/dl)	39 (13)	35 (13)	p < 0·05
Smoking habits:			NS
Smokers	n = 46 (35%)	n = 17 (27%)	
Ex-smokers	n = 38 (24%)	n = 20 (31%)	
Non-smokers	n = 47 (36%)	n = 23 (36%)	
Number of diseased vessels.			p < 0·001
1	n = 74 (57%)	n = 17 (27%)	
2	n = 31 (24%)	n = 25 (39%)	
3	n = 26 (20%)	n = 22 (34%)	
Coronary score	7·1 (5·3)	8·7 (5·5)	p < 0·01
LV-EF (%)	58 (20)	54 (22)	NS

Group 1, patients with stable angina; group 2, patients with unstable angina; BP, blood pressure; LV-EF, left ventricular ejection fraction.

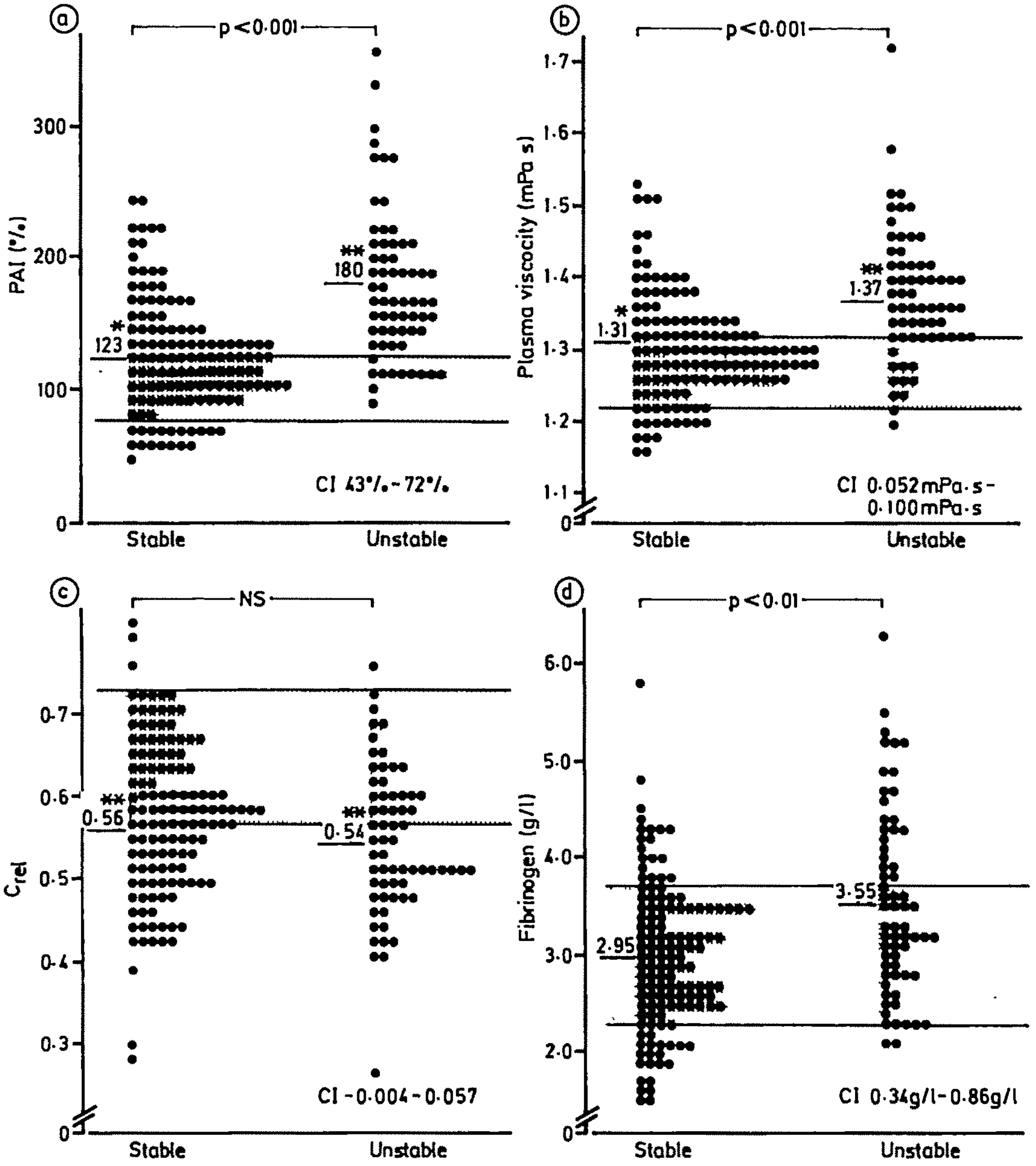


Fig 1 *Haemorrheological variable (a–c) and plasma fibrinogen concentration (d) in stable (group 1) and in unstable angina pectoris (group 2). The means for each group are shown as numerical values and are indicated graphically by horizontal lines. The hatched area represents mean ± standard deviation of normal controls. The level of significance for the difference in means between a study group and the control group is indicated* $^{*}p < 0{\cdot}05$; $^{**}p < 0{\cdot}001$. C_{rel}, *relative conductance of the microsieve at 200 Pa; CI, 95% confidence interval for the difference in means between group 1 and 2; PAI, photometric erythrocyte aggregation index.*

Table 2 *Drug treatment in the study population (number (%))*

Treatment	*Group 1 (n = 130)*		*Group 2 (n = 64)*		
β Blocking agents	113	(86)	62	(97)	p < 0·05
Calcium antagonists	94	(72)	47	(73)	NS
Nitrates:					p < 0·01
Long acting oral	101	(77)	52	(81)	
Intravenous	0	(0)	9	(14)	
Aspirin	14	(11)	62	(97)	p < 0·001

Group 1, patients with stable angina, group 2, patients with unstable angina.

erythrocyte aggregation indices (p < 0·001) (fig 1 a), and fibrinogen concentrations (p < 0·001) (fig 1 d) were significantly higher in patients with unstable angina than in patients with stable angina. The differences between the sample means in stable and unstable angina were 0·060 mPa·s (95% CI 0·052–0·100 mPa·s) for plasma viscosity, 59% with a 95% confidence interval from 43% to 72% for the photometric erythrocyte aggregation index, and 0·60 g/l with a 95% confidence interval from 0·34 g/l to 0·86 g/l for fibrinogen. There was no significant difference in haematocrit or erythrocyte filterability (fig 1 c) between the two study groups. In both study groups, mean plasma viscosity and mean photometric aggregation index were significantly higher than in the controls, while mean erythrocyte filterability was significantly diminished. Fibrinogen concentrations were significantly increased only in patients with unstable angina. Haematocrit was not different in the three groups.

RELATION OF RISK FACTOR PROFILE AND ANGIOGRAPHIC DATA TO HAEMORRHEOLOGICAL VARIABLES

Multiple linear regression (table 3) showed that the risk factor profile (mean aortic pressure, smoking habits, serum triglycerides, cholesterol, high density lipoprotein cholesterol, and plasma fibrinogen) and angiographic data (coronary score, left ventricular ejection fraction) accounted for 24% of the variability in plasma viscosity, for 32% of the variability in photometric erythrocyte aggregation index, and for 7% of the variability in erythrocyte filterability. The only variables that significantly influenced haemorrheological variables were: fibrinogen which affected plasma viscosity and the photometric erythrocyte aggregation index; to a minor extent triglycerides, which affected plasma viscosity; and mean aortic pressure, which affected erythrocyte filterability.

LOGISTIC REGRESSION

We analysed three models of stepwise logistic regression with unstable angina as the dependent variable. The first model included the haemorrheological variables (plasma viscosity, photometric erythrocyte aggregation index, erythrocyte filterability, fibrinogen level) as independent variables. Fibrinogen was eliminated because it had a negligible additional influence. Figure 2 shows the discrimination between stable and unstable angina achieved by the first model. Maximal discrimination for recognising unstable angina gave a sensitivity of 78·1% (50/64) and a specificity of 72·3% (94/130). This was accomplished with a cut off point of 0·31 for the estimated probability of unstable angina. Calculation of the same model in which we considered only cases with complete data for risk factors and angiographic variables gave similar results—at a cut off point of 0·31 the sensitivity for unstable angina was 76·6% (36/47) and the specificity was 75·3% (73/97). Again fibrinogen provided no significant information in addition to the other variables in the model.

Table 3 *Multiple linear regression*

	Dependent variable					
	Viscosity: $r^2 = 0·238$		*PAI: $r^2 = 0·315$*		*C_{rel}: $r^2 = 0·074$*	
	Independent variable					
	Partial r^2	*p*	*Partial r^2*	*p*	*Partial r^2*	*p*
Fibrinogen	0·09	0·01	0·20	0·01	0·03	0·06
Triglycerides	0·05	0·01	0·00	0·63	0·00	0·94
Cholesterol	0·00	0·81	0·01	0·14	0·01	0·22
High density lipoprotein cholesterol	0·01	0·19	0·01	0·10	0·01	0·39
Mean blood pressure	0·00	0·63	0·01	0·24	0·03	0·04
Smoking habits	0·01	0·35	0·00	0·61	0·00	0·67
Coronary score	0·02	0·09	0·00	0·61	0·00	0·54
Ejection fraction	0·01	0·20	0·01	0·10	0·00	0·59

r^2, coefficient of determination for the model containing all independent variables; partial r^2, partial coefficient of determination for the model containing all independent variables; C_{rel}, relative conductance of the microsieve at 200 Pa; PAI, photometric aggregation index.

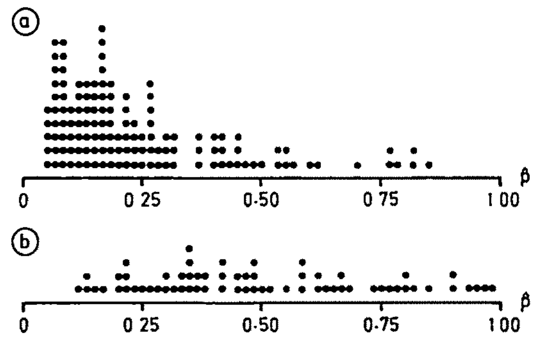


Fig 2 *Results of the stepwise logistic regression for unstable angina with plasma viscosity, photometric erythrocyte aggregation index, erythrocyte filterability, and fibrinogen concentration as independent variables (after elimination of fibrinogen concentration). (a) Predicted probabilities of unstable angina for group 1 (stable angina). (b) Predicted probabilities of unstable angina for group 2 (unstable angina).*

The second model included the haemorrheological variables in the first model as well as risk factors (mean aortic pressure; smoking habits; and plasma concentrations of triglycerides, cholesterol, and high density lipoprotein cholesterol) and angiographic variables (coronary score, left ventricular ejection fraction) as independent variables. Smoking habits, fibrinogen concentrations, and lipid concentrations were eliminated from the model because their additional influence was negligible. Discrimination was greatest at a cut off point of 0·31 for the estimated probability of unstable angina (sensitivity 78·7% (37/47) and specificity of 76·3% (74/97)).

The third model included risk factors and angiographic data as independent variables. The following variables were eliminated because they made an insignificant additional contribution to the regression: triglycerides, high density lipoprotein cholesterol, smoking habits, and left ventricular ejection fraction. Discrimination was greatest at a cut off point of 0·31 for the estimated probability of unstable angina—with a sensitivity of 63·8% (30/47) and a specificity of 63·9% (62/97).

Discussion

This study is the first to show a relation between impaired blood fluidity and the clinical manifestation of coronary artery disease, independent of the extent of coronary atherosclerosis, left ventricular function, and risk factor profile.

HAEMORRHEOLOGICAL ALTERATIONS

Chronic coronary artery disease is associated with changes in plasma viscosity, erythrocyte aggregation, and erythrocyte filterability that impair blood fluidity. Plasma viscosity and erythrocyte aggregation were higher in unstable angina than in stable angina. These haemorrheological abnormalities can be used to predict unstable angina: 78·1% of the patients with unstable angina were correctly identified by a logistic regression model that included plasma viscosity, erythrocyte aggregation, and erythrocyte filterability.

RELATION TO RISK FACTOR PROFILE AND ANGIOGRAPHIC DATA

The relation between haemorrheological variables and unstable angina was independent of differences in risk profile and angiographic data between the groups with unstable and stable angina. This conclusion is supported by two lines of evidence. Firstly, the accuracy of the logistic regression model for unstable angina that included risk factors and angiographic data improved when the haemorrheological variables were added, whereas the accuracy of the model with haemorrheological variables was not significantly improved by the inclusion of risk factors and angiographic data. Secondly, risk factors and angiographic variables had little influence on multiple linear regression for the haemorrheological variables; and most of this influence was attributable to fibrinogen. The logistic regression model including haemorrheological variables and fibrinogen, however, did not improve the discrimination between stable and unstable angina as compared with a regression model including just the haemorrheological variables. The same was true for triglycerides, one of the two other variables with a significant influence on one of the haemorrheological variables. The second, mean blood pressure, was retained in the logistic regression model. None the less, mean blood pressure accounted for only 3% of the variability in erythrocyte filterability and was not significantly related to plasma viscosity or red cell aggregation.

INFLUENCE OF THE METHOD

Apparent whole blood viscosity as a function of shear has been widely used in previous studies; the advantage of this approach is that it assesses the combined rheological effects of all blood constituents. Apparent whole blood viscosity as it is measured in rotational viscometers, however, only reflects the blood flow behaviour in large conductance vessels, which contribute little to vascular resistance.[27] Furthermore, at low shear stresses the results of apparent whole blood viscosity may be erroneous because of considerable artefacts caused by phase separation within the viscometer.[28 29] For these reasons, in the present study we analysed the haemorrheological factors that directly interfere with flow in the microcirculation.[27,30] Among these factors those of major importance are systemic haematocrit, plasma viscosity, erythrocyte aggregation, and erythrocyte deformability.[27,30,31]

Drug treatment was not standardised in the present study; hence, antianginal treatment was intensified with increasing clinical severity of the disease. In various studies, nitrates,[32,33] calcium antagonists,[34,35] and β blocking agents[36–39] were found to have no effect or even a beneficial effect on blood fluidity. Similarly, aspirin had no effect on erythrocyte deformability and whole blood viscosity.[40] Thus the haemorrheological alterations seen in patients with stable and unstable angina cannot be attributed to drug treatment.

Several groups described fibrinogen as an important haemorrheological variable because of its influence on plasma viscosity and, in particular, on erythrocyte aggregation.[6,28,29] Furthermore, fibrinogen was identified as a cardiovascular risk factor.[41] In the present study fibrinogen was, therefore, treated as a cardiovascular risk factor in the multiple linear regression, in order to assess the interrelated influence of the various risk factors on the haemorrheological variables. Because the relation between unstable angina and raised values for haemorrheological variables might only be caused by increased fibrinogen concentrations, fibrinogen was included in the logistic regression analysis as well as the haemorrheological variables.

PATHOGENETIC IMPLICATIONS

Unstable angina is associated with changes in blood properties affecting not only coagulability[42] and platelet function,[43] but also blood fluidity, as shown in the present study. Secondary effects caused by changes in risk factor profile, angiographic severity of coronary artery narrowing, or left ventricular function are excluded by the present study.

Never the less, the present study does not resolve the principal question, which is "are the haemorrheological changes associated with unstable angina a cause or an effect of the disease"? The haemorrheological changes in patients with unstable angina may be partly related to an acute phase response[12,13,44] caused by ischaemic myocardial injury. Fibrinogen, one of the acute phase reactants,[12,13] is known to enhance plasma viscosity and, in particular, erythrocyte aggregation.[28,29] In the present study, only 9% of the variability in plasma viscosity and only 20% of the variability in erythrocyte aggregation were attributed to changes in fibrinogen concentration. Furthermore, multiple logistic regression showed that the relation between plasma viscosity and erythrocyte aggregation and unstable angina was much closer than that with fibrinogen concentration. The haemorrheological alterations, therefore, could have a direct impact on unstable angina. Patients with unfavourably altered haemorrheological variables might be at increased risk of developing unstable angina superimposed on the stable course of the disease. This view is supported by experimental data showing that at low perfusion pressures, as in the post-stenotic areas, a rise in blood viscosity further curtails capillary perfusion.[4] The haemorrheological abnormalities in unstable angina may, therefore, further impede flow of nutrients in the post-stenotic myocardial microcirculation.

The study was supported by a grant from the Wilhelm Sander-Stiftung, Munich, Federal Republic of Germany.

References

1 Dormandy JA. Influence of blood viscosity on blood flow and the effect of low molecular weight dextran. *Br Med J* 1971;iv:716–9.

2 Wells R. Microcirculation and coronary blood flow. *Am J Cardiol* 1972;29:847–50.

3 Chien S. Hemorheology in clinical medicine *Clin Hemorheol* 1982;2:137–42.

4 Most AS, Ruocco NA, Gewirtz H. Effect of a reduction in blood viscosity on maximal myocardial oxygen delivery distal to a moderate coronary stenosis. *Circulation* 1986;74:1085–92.

5 Finch CA, Lenfant C. Oxygen transport in man. *N Engl J Med* 1972;286:407–9.

6 Lowe GDO, Drummond MM, Lorimer AR, *et al.* Relation between extent of coronary artery disease and blood viscosity. *Br Med J* 1979;i:673–4.

7 Fuchs J, Weinberger I, Rotenberg Z, *et al.* Plasma viscosity in ischemic heart disease. *Am Heart J* 1984; 108:435–9.

8 Low J, Dodds AJ, McGrawth M, Biggs JC. Red cell deformability and other haemorrheologic variables in stable coronary artery disease. *Thromb Res* 1985;38: 269–74.

9 Rainer CR, Kawanishi DT, Chandaratna AN, *et al.* Changes in blood rheology in patients with stable angina pectoris as a result of coronary artery disease. *Circulation* 1987;76:15–20.

10 Jan KM, Chien S, Bigger JT. Observations on blood viscosity changes after myocardial infarction. *Circulation* 1975;51:1079–84.

11 Dodds AJ, Boyd MJ, Allen J, Bennett ED, Flute PT, Dormandy JA. Changes in red cell deformability and other haemorrheological variables after myocardial infarction. *Br Heart J* 1980;44:508–11.

12 Kushner I. The phenomenon of the acute phase response. *Ann NY Acad Sci* 1982;389:39–48.

13 Dinarello CA. Interleukin I and the pathogenesis of the acute-phase response. *N Engl J Med* 1984;**311**: 1413–8.

14 Leonhard H, Arntz HR, Klemens UH. Studies of plasma viscosity in primary hyperlipoproteinaemia. *Atherosclerosis* 1977;**28**:29–40.

15 Lowe GDO, McArdle BM, Stromberg P, Lorimer AR, Forbes CD, Prentice CRM. Increased blood viscosity and fibrinolytic inhibitor in type II hyperlipoproteinaemia. *Lancet* 1982;**i**:472–5.

16 Letcher RL, Chien S, Pickering TG, Laragh JH. Elevated blood viscosity in patients with borderline essential hypertension. *Hypertension* 1983;**5**:757–62.

17 Isles C, Lowe GDO, Rankin BM, *et al.* Abnormal haemostasis and blood viscosity in malignant hypertension. *Thromb Haemost* 1984;**52**:253–5.

18 Belch JJ, McArdle BM, Burns P, Lowe GDO, Forbes CD. The effects of acute smoking on platelet behaviour, fibrinolysis and haemorrheology in habitual smokers. *Thromb Haemost* 1984;**51**:6–8.

19 Kohlmeier M. Simplified lipoprotein analysis by means of ultracentrifugation. *Arztl Lab* 1986;**32**:46–52.

20 Judkins MP. Selective coronary angiography: a percutaneous transfemoral technique. *Radiology* 1967;**89**: 815–24.

21 Harkness J. A new instrument for the measurement of plasma viscosity. *Lancet* 1963;**ii**:280–1.

22 Volger E, Schmid-Schonbein H, VonGosen J, Klose HJ, Kline KA. Microrheology and light transmission of blood. IV. The kinetics of artificial red cell aggregation induced by dextran. *Pflugers Arch* 1975; 354:319–37.

23 Kiesewetter H, Radtke H, Schneider R, Mussler K, Scheffler A, Schmid-Schönbein H. The mini-aggregometer: a new apparatus for the rapid quantification of the extent of erythrocyte aggregation. *Biomed Tech (Berlin)* 1982;**27**:209–13.

24 Teitel P. Basic principles of the filterability test and analysis of erythrocyte flow behavior. *Blood Cells* 1979;**3**:55–70.

25 Neumann FJ, Haupt H, Zimmermann R, Tillmanns H. Metal microsieves in red cell filtration. *Clin Hemorheol* 1989;**9**:125–37.

26 Clauss A. Gerinnungsphysiologische Schnellmethode zur Bestimmung des Fibrinogens. *Acta Haematol (Basel)* 1957;**17**:237–42.

27 Schmid-Schönbein H. Microrheology of erythrocytes, blood viscosity and the distribution of blood in the microcirculation. In: Guyton AC, Cowley AW, eds. *International Reviews in Physiology vol 9. Cardiovascular physiology II*. Baltimore: University Park Press, 1976:1–62.

28 Merrill EW. Rheology of blood. *Physiol Rev* 1969;**49**: 863–88.

29 Chien S, Usami S. Shear dependent interactions of plasma proteins with erythrocytes in blood rheology. *Am J Physiol* 1970;**219**:143–53.

30 Schmid-Schönbein H, Rieger H, Fischer T. Blood fluidity as a consequence of red cell fluidity: flow properties of blood and flow behavior of blood in vascular diseases. *Angiology* 1980;**31**:301–19.

31 Schmid-Schönbein H, Gallasch G, von Gosen J, Volger E, Klose HJ. Red cell aggregation in blood flow. II. Effect on apparent viscosity of blood. *Klin Wochenschr* 1976;**54**:159–67.

32 Hossmann V, Wegener H, Wegener B, Saborowski F, Cäsar K. Hemorrheological and hemodynamic effects of ISDN in essential hypertension and obliterative arterial disease. In: Lichtlen PR, Enge HJ, Schrey H, Swan HJC, eds. *Nitrates III*. Berlin, Heidelberg, New York: Springer, 1981:263–70.

33 Ehrly AM, Landgraf H. Einfluß von Isosorbitdinitrat auf die Fliesseigenschaften des Blutes bei Patienten mit chronischer arterieller Verschlusskrankheit. In: Ehrly AM, ed. *Therapie mit hämorheologisch wirksamen Substanzen*. Munich, Berne, Vienna: Zuckerschwerdt, 1984:145–8.

34 Volger E, Pfafferott C, Bauersachs R, Busch U, Gaim F, Stoiber M. Hemorrheological aspects of myocardial ischaemia. *Clin Hemorheol* 1986;**6**:229–43.

35 Volger E, Schönharl B, Haberland S, Pfafferott C. Effect of different calcium antagonists on red blood cell filterability [Abstract]. *Biorheol* 1986;**23**:243.

36 Boogaerts MA, Roelant C, Temmermann J, Goosens W, Verwilchen RL. Effect of beta-blocking drugs on red cell adhesive and rheological properties. *J Lab Clin Med* 1983;**102**:899–908.

37 Caimi G, Catania A, Frazzeta F, Capobianco D, Sarno A. The behaviour of the hemorrheological determinants and their trends during beta-blocker treatment. *Jpn Heart J* 1973;**24**:723–9.

38 Ernst E, Roloff C, Marshall M. Beta-blocker increases blood fluidity. *Herz und Gefässe* 1984;**4**:470–9.

39 Waller DG. Whole blood viscosity following cardioselective beta-adrenoreceptor blockade in hypertension. *Clin Hemorheol* 1982;**2**:243–7.

40 Stäubli M, Reinhard W, Straub PW. Blood viscosity and red cell deformability after aspirin in vivo—a double blind controlled trial. *Atherosclerosis* 1982; 41:167–70.

41 Kannel WB, Wolf PA, Castelli WP, D'Agostino RB. Fibrinogen and risk of cardiovascular disease. *JAMA* 1987;**258**:1183–6.

42 Throux P, Latour JG, Lger-Gauthier C, Delara J. Fibrinopeptide A and platelet factor levels in unstable angina pectoris. *Circulation* 1987;**75**:156–62.

43 FitzGerald DJ, Roy L, Catello F, FitzGerald GA. Platelet activation in unstable coronary disease. *N Engl J Med* 1986;**315**:983–9.

44 Stuart J. The acute phase reaction and haematological stress reaction and haematological stress syndrome in vascular disease. *Int J Microcirc* 1984;**3**:11–9.

Br Heart J 1989;62:429–37

Estimation of the risk of death during the first year after acute myocardial infarction from systolic time intervals during the first week

B J NORTHOVER

From the Leicester Royal Infirmary, Leicester

SUMMARY Patients who survived for the first seven days after acute myocardial infarction were followed up for a further 51 weeks. During these 51 weeks there were 123 deaths and 477 eventual survivors. Approximately half of the deaths occurred during the first 3 weeks of follow up. The deaths were predicted with 75% sensitivity and 73% specificity by a discriminant analysis based upon six variables seen during the first 7 days; predictions of death and survival were 55% and 92% accurate respectively. These six variables were, in ascending order of prognostic importance, the occurrence of bundle branch blocks, the administration of a diuretic, the age of the patient, the presence of diabetes mellitus, a previous myocardial infarction, and the ratio of the measured left ventricular pre-ejection and ejection periods. Many other monitored variables, although univariately associated with death, contributed nothing further to the multivariate assessment of mortality risk.

Most deaths from myocardial infarction occur within the first few days. Nevertheless, patients who survive for a week in hospital remain at increased risk of death, albeit diminishing risk, for several months thereafter.[1 2] Many such delayed deaths, although not all, occur suddenly and outside hospital. Most are considered to be caused by cardiac arrhythmias.[3 4] Approximately 16% of patients who currently leave hospital alive after acute myocardial infarction die during the remainder of the first year.[5] Prophylactic agents intended to reduce this delayed mortality are available.[6] Such agents would best be confined, however, to the subgroup of individuals at greatest risk of death during the first few months after infarction. But can the high risk subgroup of patients be identified while still in hospital?

Numerous features have been shown to be statistically associated with subsequent death,[7] but to varying degrees in different reported series. This is particularly true of cardiac rhythm disturbances that occur while patients are in hospital.[8 9] Disagreement continues about whether arrhythmias constitute prognostically adverse features operating independently of those other adverse features that often coexist.[10–12] Left ventricular failure, on the other hand, has been shown consistently to be independently associated with death.[13–15] Nevertheless, little information is available on which haemodynamic feature of cardiac failure, which test for its presence, and which measure of its severity are prognostically most reliable. Moreover, the time after infarction at which collection of this information is most meaningful is presently unknown. These matters were investigated in the present study, with an emphasis upon observations and tests that are sufficiently safe and easy to use for them to be available in even a non-specialist general hospital, and which were applicable within the first week to all patients, irrespective of age, severity of infarction, or the presence of concomitant disease. Early assessment is essential because many patients die within a few weeks of discharge.[1] Furthermore, the procedures used must be applicable to even the oldest and frailest patients because they are the most likely to die.[5]

Patients and methods

Patients admitted to the Leicester Royal Infirmary who fulfilled the World Health Organisation's

Requests for reprints to Dr B J Northover, Coronary Care Unit, Leicester Royal Infirmary, Leicester LE1 5WW.

Accepted for publication 10 August 1989

criteria for a "definite acute myocardial infarction"[16] and who survived for the first 7 days were studied prospectively for the remainder of the first year. A total of 600 consecutive episodes of infarction, all managed by the same consultant, form the basis of this report. No eligible patient was excluded during the study period. The policies and techniques used for monitoring and managing such patients in this hospital, both in the coronary care unit and after transfer to general medical wards, have been described previously.[17 18] No patient received thrombolytic treatment. On each of the first 2 or 3 days in hospital the following routine tests and investigations were performed on all patients: (*a*) a chest radiograph was obtained with a mobile *x* ray source; (*b*) a standard 12 lead electrocardiogram was recorded; (*c*) venous blood serum was analysed for creatine kinase, hydroxybutyrate dehydrogenase, alkaline phosphatase, glutamyl transferase, bilirubin, urea, creatinine, urate, sodium, potassium, bicarbonate, calcium, and phosphate; and (*d*) left ventricular systolic time intervals were measured on a simultaneously recorded electrocardiogram, phonocardiogram, and externally registered carotid artery pulse, as described in detail elsewhere.[17 18] The ratio of left ventricular pre-ejection and ejection periods (PEP/EP) is known to have the greatest prognostic value.[17 18] This ratio also has the convenience of being largely independent of heart rate. The PEP/EP ratios were already known to divide patients at the time of admission to this hospital into five prognostic strata with mortalities ranging from 4% to 62% during the first 7 days.[17 18] These same strata were used in the present study. Anatomical site of infarction was classified electrocardiographically by familiar but arbitrary criteria.[19 20]

Patients were routinely examined every day by me while they were in hospital, and I paid particular attention to features of cardiac failure (table 1). On day 5 PEP/EP ratios were remeasured in all patients and an electrocardiogram was tape recorded for 24 hours on all patients. I analysed tape recordings by procedures that have been described and validated previously.[21] Most disturbances of rhythm were classified according to the criteria of Schamroth[22] (table 2). Intraventricular conduction defects, however, were classified according to the World Health Organisation's criteria,[23] except that fascicular blocks were ignored. Tape recorded ventricular extrasystoles and paroxysms of ventricular tachycardia were graded in various ways (table 2), including that proposed by Lown and Wolf.[24]

A signal averaged electrocardiogram was obtained from 506 patients during the fifth day in hospital. Frank orthogonal bipolar leads X, Y, and Z were recorded simultaneously for 10 min with the patient at rest. Averaging was performed by the methods of Simson[25] with a commercially available system (model 101, made by Arrhythmia Research Technology of Oklahoma). Averaging was not attempted in the remaining 94 patients who had atrial fibrillation, atrial flutter, bundle branch blocks,[26] or extrasystoles occurring at a frequency of > 10/min. Less frequent extrasystoles were automatically deleted by a template algorithm within the computer program. At least 200 sinus beats were bidirectionally bandpass-filtered between 25 and 250 Hz. This provided a noise level of $< 1 \mu V$ in all cases. A root mean square voltage in the final 40 ms of the averaged QRS complex of $\leqslant 25 \mu V$ or an averaged QRS duration of $\geqslant 120$ ms was taken to be a significant late potential.[25]

No patient was lost to follow up, which was from the beginning of day 8 to the end of day 365. Surviving patients were seen in outpatient clinics for as long as this was required clinically. Thereafter I contacted patients. All medications, investigations, and operations were documented during follow up, as were further myocardial infarctions, diagnosed according to the same criteria used for the index infarction. Exercise electrocardiography was undertaken by 113 patients, predominantly younger men, a median of 22 weeks after infarction. The results of this test were not used in the statistical analysis of this study because no patient who died had taken the test, a pattern noted previously by others.[7 9] Coronary angiography was performed on 29 patients after infarction (median 37 weeks), although only six patients had coronary angioplasty or aorto-coronary bypass surgery during follow up.

Death was the primary patient end point that I studied. All hospital records relating to the period of follow up were scrutinised, but many of the deaths occurred outside hospital, usually at home. In such cases the person who witnessed the event was contacted, or failing that the person who discovered or certified death. Information was routinely collected on the date and time of death, the patient's activities before death, and the time that elapsed between any premonitory events and death.

All the routinely monitored variables, as defined in tables 1–3, from all 600 patients in the study were categorised for statistical analysis into two or more bands—most often simply presence or absence. More complex categories are defined in the text and tables. Statistical associations between all possible pairs of routinely monitored variables and between each monitored variable and patient end point were then assessed by χ^2 tests plus a stepwise linear discriminant analysis contained in the *Statistical Package for the Social Sciences*.[27] This permitted both univariate and multivariate associations to

Table 1 *Routinely monitored variables that may be related to the effectiveness of cardiac pumping*

	Numbers of patients	
	With feature	*With feature who died*
Lung crepitation:		
Day of admission	—	—
Day of discharge*	32	13
Any day*	293	75
Above lower scapular margin on any day*	74	23
Gallop rhythm (i) third, (ii) fourth, (iii) summation.		
Day of admission (*for i and iii)	58 (i or iii)	19
Day of discharge (*for i and iii)	66 (i or iii)	25
Any day (*for i and iii)	81 (i or iii)	28
Cardiac apical impulse on day 5:		
Palpability	—	—
To left of mid-clavicular line (cm)	—	—
Dyskinetic	—	—
Diameter > 4 cm*	110	35
Jugular pulsations > 3 cm above sternal notch*	115	40
Oedema on any day:		
Feet or ankles*	67	24
Above mid-calf*	26	11
Sacral	—	—
Blood urea > upper limit of normal range:		
Day of admission*	162	53
Maximum in hospital*	280	75
Anterior-posterior radiograph at admission		
Pulmonary venous imbalance*	204	59
Pulmonary oedema*	59	20
Pleural effusion*	22	13
Radiographic evidence on any day		
Pulmonary venous imbalance*	213	61
Pulmonary oedema*	71	35
Pleural effusion*	70	40
Maximum cardiothoracic ratio > 0·5 on any day†*	220	68
Killip and Kimball class[30] categorised in 4 grades		
Day of admission*	273 (≥2)	77
Worst score in hospital*	296 (≥2)	78
Prognostic index of Norris and co-workers,[5] categorised as < 3, 3–5, 6–8, 9–11, or > 11		
Day of admission*	265 (≥3)	75
Worst score in hospital*	304 (≥3)	82

*Indicates a significant univariate association with non-survival. All features were categorised as present or absent unless specified otherwise †Indicates radiographic information derived from an erect posterior-anterior film with the x ray source 6 feet from the chest.

be assessed, with $p < 0.05$ being regarded as significant. This method for predicting outcome after myocardial infarction is well established.[28-30]

As progressively more patients completed their year of follow up it became possible by means of discriminant analyses to calculate on day 7 the probability that each subsequently enrolled patient would survive for a year, based upon multivariate comparison of the patient's own characteristics with those of all preceding patients in the study. At the end of the year of follow up the actual and predicted outcomes were compared. Predictions only became maximally successful, however, after the first 190 patients had completed their follow up.

Results

A total of 123 patients died during follow up (20% of the study population); 61 of the deaths occurred within the first month. Time of death was known to the nearest hour in 95 patients. Of the accurately timed deaths, 39 occurred between 05.00 h and 11.00 h, which is significantly more than occurred during any other consecutive 6 h period, confirming previous findings.[31] No consistent pattern of antecedent activities or premonitory events was discovered. Death seemed to be unexpected in 57% whose death was witnessed.

Many of the routinely monitored variables in the present study, as defined in tables 1–3, were univariately associated with death. This was expected because the variables had been chosen because an association with death was envisaged. Discriminant analysis was performed to identify which routinely monitored variables were multivariately predictive of death. When all routinely monitored variables were included predictions were 75% sensitive and 73% specific, with the predictive accuracy of death and survival being 55% and 92% respectively. Each monitored variable was then omitted in turn in

Table 2 *Disturbances of ventricular rhythm routinely tape recorded on day 5*

Feature	*Numbers of patients* With feature	*Numbers of patients* With feature who died
VEs ≥ 1/hour*	117	36
Multifocal VEs	85	25
Paired VEs	64	21
VEs in bigeminy	79	28
Early VEs (RR′/QT < 1)	—	—
AIVR	28	11
VT	57	19
Highest VT rate (100–200/min or >200/min)	—	—
Number of paroxysms of VT	—	—
Longest paroxysm of VT (beats and seconds)	—	—

Arrhythmias were classified as present or absent unless specified above. With the exception of early VEs, all other listed features were univariately significantly associated with PEP/EP ratios on day 5 and with death

*VEs, ventricular extrasystoles. Values of 1–10 VEs/hour and > 10 VEs/hour were also univariately associated with death.

AIVR, accelerated idioventricular rhythm (≥3 consecutive QRS complexes at <100/min)

VT, ventricular tachycardia (≥3 consecutive QRS complexes at ≥ 100/min)

reverse order of closeness of univariate association with death. Most single variables could be omitted without reducing the predictive sensitivity, specificity, or accuracy. One by one such variables were eliminated until only six remained. These six variables were, in diminishing order of their respective standardised canonical discriminant function coefficients[30] (used here as a convenient measure of prognostic impact): (*a*) the PEP/EP ratio on day 5 categorised as <0·30 = 1, 0·30–0·33 = 2, 0·34–0·37 = 3, 0·38–0·41 = 4, >0·41 = 5; (*b*) the number of previous myocardial infarctions (MI) the patient was known to have sustained, diagnosed by the same criteria that were used for the index infarction; (*c*) whether the patient had diabetes mellitus (DM) categorised as present = 1, absent = 0; (*d*) the age group in years of the patient, categorised as <40 = 3; 40–50 = 4, 51–60 = 5, 61–70 = 6, 71–80 = 7, and >80 = 8; (*e*) whether a diuretic drug with a direct renal action was administered at any stage in hospital, categorised as used = 1, not used = 0; and (*f*) whether right or left bundle branch block (BBB) was shown while in hospital, categorised as shown = 1, not shown = 0. In combination these six variables were as successful as the combination of all the routinely monitored variables. These six variables could be combined in the following equation: Risk = 0·61 (PEP/EP) + 0·92 (MI) + 0·93 (DM) + 0·28 (age group) + 0·53 (diuretic) + 0 28 (BBB). Each term in this equation is the product of the non-standardised canonical discriminant function coefficient for that variable and the patient's own value for the variable. Where the risk was >2·73 the patient had >50% chance of death during follow up and was classed as a predicted non-survivor. Patients with a <30% chance of death during follow up had a calculated risk of <2·31, and those with a <10% chance of death had a calculated risk of <2·04.

Discriminant analysis with uncategorised values for age and the PEP/EP ratio gave essentially the same mortality predictions as those using the categories defined above. Categorised data, however, simplified the calculation of risk, even to the point of making it possible by mental arithmetic.

Any multivariate analytical technique makes certain assumptions about the numerical distribution of the data it is called upon to handle. If the assumptions are not fulfilled the predictive effective-

Table 3 *Probabilities that the univariate associations between the monitored variables and outcomes were due to chance*

	PEP/EP	*MI*	*DM*	*Age group*	*Diuretic*	*BBB*
Non-survival	<0·001*	<0·001*	0·001*	0·001*	<0·001*	<0·001*
PEP/EP		<0·001	0·047*	<0·001*	<0·001*	<0·010*
MI			0·230	0·990	0·003*	0·297
DM				0·185	<0·001*	0·149
Age group					0·002*	0·059
Diuretic						0·005*

PEP/EP, ratio of pre-ejection and ejection periods on day 5 (≥0·30 in 257, of whom 96 died); MI, number of previous myocardial infarctions (≥1 in 117, of whom 48 died); DM, diabetic status (121 diabetic patients, of whom 39 died); Age group, age in years, by decade (159 patients >70 years, of whom 50 died); Diuretic, treatment with a diuretic drug while in hospital (317 treated patients, of whom 92 died), BBB, right and left bundle branch blocks while in hospital (present in 92, of whom 35 died) *Univariate association between the indicated variables was significant ness may be reduced. The data derived from the present study were re-examined, therefore, by two additional techniques, namely logistic regression and the Cox model. The same six routinely monitored variables (table 3) were most predictive of mortality in all three methods of analysis. The Cox model, however, identified third degree atrioventricular block as a seventh independent contributor, but this was of marginal significance. Logistic regression was slightly less sensitive (73%) than discriminant analysis and the Cox model was slightly less specific (70%) than either discriminant analysis or logistic regression. Because of the slight predictive superiority of discriminant analysis I have used this for the remainder of this report.

Despite statistical independence for predictive purposes, each of the six variables listed in table 3 was also highly associated univariately with at least one of the other five. Patients who died without any warning were very similar in terms of these six variables to patients whose death came more gradually or after particular patterns of premonitory events. Only two patients died from apparently non-cardiac causes; one had a cerebrovascular accident and the other died of carcinomatosis.

Most of the routinely monitored variables in the present study owed whatever univariate association with death that they had (tables 1 and 2) to being associated with one or more of the six primary variables listed in table 3. For example, many of the monitored variables reflecting reduced pumping effectiveness of the left ventricle (table 1) were closely associated univariately with death but contributed nothing additional to PEP/EP ratios on day 5 in the multivariate assessment of risk. This was also true of PEP/EP values measured on days other than day 5. There was a univariate association between death and infarction of the anterior wall, compared with other sites, but this feature also failed to contribute multivariately to mortality risk.

Only one routinely monitored variable reflecting ventricular pumping effectiveness was found to be predictive of death independently of PEP/EP values on day 5, and that was diuretic use (table 3). This remained true irrespective of whether diuretic use was defined in terms of day of admission only, the last day in hospital, or indeed any day or combination of days in hospital. It was also independent of the type of diuretic used, the dose used, or the route by which it was administered. The highest standardised canonical discriminant function coefficient was obtained when this variable was defined in terms of "at any time in hospital", and it is in this sense that the variable is used in the remainder of this report. Diuretic usage was only marginally less predictive of death, however, when use on only the first day in hospital was considered.

Several disturbances of cardiac rhythm recorded on the routine daily 12 lead electrocardiograms, plus those on the routinely tape recorded electrocardiogram on day 5, were univariately associated with death. This was true of episodes of second and third degree atrioventricular block, of atrial fibrillation, of atrial flutter, and of all forms of supraventricular tachycardia combined. Ventricular extrasystoles on the tape recorded electrocardiogram were univariately associated with death, and the association was closest when the frequency of these beats was categorised as <1, 1–10, or >10 per hour (table 2). Table 2 shows several other features of the ventricular extrasystoles, such as grading according to the scheme of Lown and Wolf[24] or occurrence in bigeminy or pairs, which although still significantly associated univariately with death, were less closely associated with this outcome than when the frequency of ventricular extrasystoles was defined as in table 2. Paroxysms of ventricular tachycardia on the tape recorded electrocardiogram had a similar prognostic significance to that of the frequency of ventricular extrasystoles. This was true irrespective of whether this arrhythmia was defined independently of the ventricular rate, or was categorised in three bands with average rates of <100, 100–200, and >200 per min. Severity attribution was to the band representing the paroxysm with the highest rate. The prognostic significance of ventricular tachycardia was independent of the length of the longest paroxysm, the average length of the recorded paroxysms, or the total number of paroxysms during the 24 hour recording (table 2). None of the forgoing arrhythmias, however, made an independent contribution to mortality risk after allowance for the six variables shown in table 3, and was seemingly independent of whether a patient was receiving antiarrhythmic drugs on day 5, or had done so earlier while in hospital.

The occurrence of supraventricular extrasystoles on the electrocardiogram tape recorded on day 5, or the occurrence of ventricular fibrillation while in hospital were not associated univariately with death during follow up.[32-34]

Late potentials were found in 168 of the 506 signal-averaged electrocardiograms and were significantly associated univariately with death. They made no independent contribution to mortality risk, however, in these 506 patients after allowance for the six variables listed in table 3. Late potentials and tape recorded paroxysms of ventricular tachycardia showed a univariate association, and both were associated univariately with frequent ventricular extrasystoles on the tape recorded electrocardiogram.

To determine whether the prognostic significance of each of the routinely monitored variables changed significantly during the study period a discriminant analysis was performed on just the first 200 patients. This predicted the first year outcomes with 74% sensitivity, 74% specificity, and 56% accuracy for death. Unstandardised canonical discriminant function coefficients were calculated for each of the monitored variables in these first 200 patients. The coefficients were then used, without modification, to predict outcome in the remaining 400 patients. Predictions made in this way were 74% sensitive, 73% specific, and 55% accurate for death.

All survival predictions presented so far in this report relate to a 51 week period of follow up. Discriminant analyses were also undertaken to examine the predictability of survival for shorter periods. The 3 month predictions were 76% sensitive, 75% specific, and 55% accurate for death, values not significantly different from the one year predictions, and with the same six variables (table 3) contributing. This was not very surprising because a substantial majority of the deaths occurred within the first 3 months.

Discussion

As in several previous reports,[13–15] patients in the present study with evidence of cardiac failure while in hospital had a high one year mortality. The most useful measure of cardiac pumping effectiveness from the list of routinely monitored variables was the ratio of the measured left ventricular pre-ejection and ejection periods on day 5. Previous workers also have reported a univariate association between this ratio in patients while in hospital and one-year non-survival,[35–38] although a multivariate study has not been published previously. Many of the classic symptoms and physical signs of cardiac failure correlated only weakly with the more objective measures, such as PEP/EP values. This too accords with previous reports.[39] A significant univariate association was found in the present study between lung crepitations heard on day 5 and PEP/EP values on that day of $>0{\cdot}33$, although not with values of 0·30–0·33. There was a significant univariate association, however, between diuretic usage while the patient was in hospital and PEP/EP values of 0·30–0·33 on day 5, as well as with higher values of this ratio. Lung crepitations, therefore, have limited prognostic value (table 1).

Evidence of pulmonary venous imbalance on the radiograph obtained routinely in the present study at the time of admission had some prognostic value. At the time this radiograph was obtained patients with even mild left ventricular failure are unlikely to have had time to respond to any diuretic medication to the extent that pulmonary venous imbalance would have gone. Indeed, in less severe cases the decision to give diuretic medication often was taken only after viewing the chest radiograph. Previous workers have noted that patients with radiographic or other objective evidence of left ventricular failure at the time of admission are more likely to die within a year of discharge,[40–42] even if the signs of failure resolve during the first few days in hospital.[43–46]

It is uncertain why diuretic usage carried an adverse prognostic significance in the present study. Electrolyte imbalance[47] is unlikely to be the whole explanation since patients who received only a single dose of a diuretic at the time of admission to hospital remained at increased risk throughout follow up, irrespective of whether any diuretic was given during follow up. Areas of ischaemic but still viable myocardium may create a low left ventricular diastolic compliance during the early stages of an infarction, and such patients would receive diuretic treatment to relieve their pulmonary congestion. Areas of myocardial stiffness are known to improve while in hospital,[48] enabling the diuretic to be stopped. The existence of areas of only marginally perfused myocardium, however, may continue to pose a risk of arrhythmias,[49] even though collateral vessels may open sufficiently to improve the diastolic stiffness.[50]

Numerous methods for assessing the pumping effectiveness of the left ventricle have been used to predict survival after myocardial infarction, notably imaging with ultrasound, radionuclides, and *x* ray contrast media. So far, however, none has been reported to predict survival with a combination of sensitivity, specificity, and accuracy[10 51 52] any better than the six variables listed in table 3.

The prognostic significance of ventricular extrasystoles and paroxysms of ventricular tachycardia on tape recorded electrocardiograms is still disputed. Paroxysms of ventricular tachycardia in one 24 hour recording are often absent the next day.[53] Furthermore, frequent and complex ventricular extrasystoles seem to possess independent prognostic significance among patients with non-Q wave infarctions but not among those with Q wave infarctions.[54] Ventricular arrhythmias are both more common and prognostically more sinister when recorded 2 weeks or more after infarction than when recorded, as in the present study, during the first week.[55] Ventricular extrasystoles have shown an independent prognostic significance when combined with a simple clinical assessment of left ventricular function plus evidence from a chest radiograph,[8 56–58] or with left ventricular ejection fractions derived from multiple gated ventriculography.[59] The prognostic significance of ejection fractions may be enhanced multivariately by including information on paroxysms of ventricular tachycardia,[3 60] on ventricular extrasystoles at a rate of >3 per hour[3] or >10 per hour,[61 62] or on the complexity of the ventricular extrasystoles.[63] These

Table 4 *Standardised canonical discriminant function coefficients calculated for the six most important monitored variables after dicotomisation*

Dicotomised variable							
Name	*Value*	*PEP/EP*	*MI*	*DM*	*Age group*	*Diuretic*	*BBB*
PEP/EP:	<0 30	(0 589)	0 341	0 560	0 348	0 424*	0 215
	>0 29		0 497	0 200	0 350	—	—
MI·	0	0·366	(0 477)	0 581*	0 429*	0 287	0 139
	>0	0 941		—	—	0 275	0 237
DM	Absent	0 640*	0·600*	(0 345)	0·385*	—	0 249*
	Present	—	—		—	0 818*	—
Age group	<7	0·552*	0 501*	0·406*	(0 281)	0 144*	—
	>6	—	—	—		—	0 726*
Diuretic.	Not given	0 939	0 596	0 185	—	(0·255)	—
	Given	0 412	0 570	0 462	0 488*		0 229*
BBB:	Absent	0 639	0 511	0 430	0 232	0 217	(0 094)
	Present	1·164	0 241	0 239	0 349	0 697*	

See footnote to table 3 for abbreviations. Values in parentheses are coefficients for undichotomised variables *Variables where the two dichotomised values gave significantly different coefficients. Missing values are variables that failed to contribute multivariately to risk of death.

arrhythmias failed to enhance the success of predictions, when, as in the present study, combined with evidence of the extent of myocardial injury derived from biplane x ray contrast ventriculography[14 15] or thallium imaging.[15] Furthermore, radionuclide derived ejection fractions when combined with clinical evidence of ventricular dysfunction were no longer prognostically enhanced by information about ventricular arrhythmias.[9 10 12] Ventricular arrhythmias, therefore, probably reflect the extent of myocardial injury. The more fully the extent of injury has already been taken account of in a multivariate assessment of risk the less will be the additional contribution from ventricular arrhythmias.[11] In one previous study,[29] as in the present investigation, bundle branch blocks contributed multivariately to the risk of death in the year after myocardial infarction. In contrast with the previous study, however, patients in the present study with right and left bundle branch blocks had a similar mortality, which allowed data from them to be combined for statistical analysis.

The present study confirms previous work[24 64] in showing that diabetes is an adverse prognostic feature that is independent of those others with which it often coexists (table 3). The adverse prognostic significance of several of the routinely monitored variables was different in diabetic and non-diabetic patients. Standardised canonical discriminant function coefficients were calculated for each of the prognostically important variables after patients were stratified in the ways shown in table 4. In contrast with the situation among non-diabetic patients only diuretic use made an independent prognostic contribution among diabetic patients and warrants further study.

As in previous studies,[29] age operated independently of the other prognostically important variables in the present study (table 3). In contrast with the situation among younger patients, however, the only routinely monitored variable that had an independent prognostic impact among those aged >70 years was the occurrence of bundle branch blocks (table 4). Note also that the age group to which a patient belonged did not make an independent contribution in those who had previously had a myocardial infarction, in the diabetics, and in those who did not receive a diuretic while in hospital (table 4). The reasons for these subgroup differences warrants further study.

In conclusion, within the first week it is possible to predict the risk of death for each patient recovering from an acute myocardial infarction. Only six items of information are required and assessment is possible entirely at the patient's bedside without resort to expensive, difficult, or dangerous investigations. Those found to be at some predetermined level of risk, say 50%, warrant prophylaxis.[6]

I thank those many members of the staff of the Leicester Royal Infirmary who have helped me during the course of this study, particularly Dr J R Hearnshaw. Andrew Curry collaborated on the mathematical aspects of the study.

References

1 Marcus FI, Cobb LA, Edwards JE, *et al.* Mechanism of death and prevalence of myocardial ischemic symptoms in the terminal event after acute myocardial infarction. *Am J Cardiol* 1988;61:8–15.

2 Gilpin EA, Koziol JA, Madsen EB, Henning H, Ross J. Periods of differing mortality distribution during the first year after acute myocardial infarction. *Am J Cardiol* 1983;52:240–4.

3 Bigger JT, Fleiss JL, Kleiger R, Miller JP, Rolnitzky LM. The relationships among ventricular arrhy-

thmias, left ventricular dysfunction, and mortality in the 2 years after myocardial infarction. *Circulation* 1984;**69**:250–8.

4 Goldstein S, Friedman L, Hutchinson R, *et al.* Timing, mechanism and clinical setting of witnessed deaths in postmyocardial infarction patients. *J Am Coll Cardiol* 1984;**3**:1111–7.

5 Norris RM, Caughey DE, Deeming LW, Mercer CJ, Scott PJ. Coronary prognostic index for predicting survival after recovery from acute myocardial infarction. *Lancet* 1970;**ii**:485–8.

6 Antiplatelet Trialists' Collaboration. Secondary prevention of vascular disease by prolonged antiplatelet treatment. *Br Med J* 1988;**296**:320–31.

7 Gottlieb SO, Gottlieb SH, Achuff SC, *et al.* Silent ischemia on Holter monitoring predicts mortality in high-risk postinfarction patients. *JAMA* 1988; **259**:1030–5.

8 Kostis JB, Wilson AC, Sanders MR, Byington RP. Prognostic significance of ventricular ectopic activity in survivors of acute myocardial infarction who receive propranolol. *Am J Cardiol* 1988;**61**·975–8.

9 Tibbits PA, Evaul JE, Goldstein RE, *et al.* Serial acquisition of data to predict one-year mortality rate after acute myocardial infarction. *Am J Cardiol* 1987;**60**:451–5.

10 Ahnve S, Gilpin E, Henning H, Curtis G, Collins D, Ross J. Limitations and advantages of the ejection fraction for defining high risk after acute myocardial infarction. *Am J Cardiol* 1986;**58**:872–8.

11 Surawicz B. Prognosis of ventricular arrhythmias in relation to sudden cardiac death: therapeutic implications. *J Am Coll Cardiol* 1987;**10**:435–47.

12 Madsen EB, Gilpin E, Henning H, *et al.* Prediction of late mortality after myocardial infarction from variables measured at different times during hospitalization. *Am J Cardiol* 1984;**53**:47–54.

13 Hakki AH, Nestico PF, Heo J, Unwala AA, Iskandrian AS. Relative prognostic value of rest thallium-201 imaging, radionuclide ventriculography and 24 hour ambulatory electrocardiographic monitoring after acute myocardial infarction. *J Am Coll Cardiol* 1987;**10**.25–32.

14 Schulman SP, Achuff SC, Griffith LSC, *et al.* Prognostic cardiac catheterization variables in survivors of acute myocardial infarction: a five year prospective study. *J Am Coll Cardiol* 1988;**11**:1164–72.

15 Taylor GJ, Humphries JO, Mellits ED, *et al.* Predictors of clinical course, coronary anatomy and left ventricular function after recovery from acute myocardial infarction. *Circulation* 1980;**62**:960–70.

16 World Health Organization. Regional Office for Europe. *Ischaemic heart disease registers: report of the fourth working group.* Copenhagen: World Health Organization, 1970:30–48

17 Northover BJ. Left ventricular systolic time intervals in patients with acute myocardial infarction. *Br Heart J* 1980;**43**:506–13.

18 Northover BJ The value of temporary electrical pacing for patients with acute myocardial infarction. *Methods Inf Med* 1984;**23**:23–8.

19 Greenberg H, Gillespie J, Dwyer EM. A new electrocardiographic classification for post-myocardial infarction clinical trials. *Am J Cardiol* 1987;**59**: 1057–63.

20 Killip T, Kimball JT. Treatment of myocardial infarction in a coronary care unit. A two-year experience with 250 patients. *Am J Cardiol* 1967; **20**:457–64.

21 Northover BJ. Ventricular tachycardia during the first 72 hours after acute myocardial infarction. *Cardiology* 1982;**69**:149–56.

22 Schamroth L. *The disorders of cardiac rhythm.* Oxford: Blackwell Scientific Publications, 1971:1–293.

23 Willems JL, Robles de Medina EO, Bernard R, *et al.* Criteria for intraventricular conduction disturbances and pre-excitation. *J Am Coll Cardiol* 1985;**5**: 1261–75.

24 Lown B, Wolf M. Approaches to sudden death from coronary heart disease. *Circulation* 1971;**44**:130–42.

25 Simson MB. Use of signals in the terminal QRS complex to identify patients with ventricular tachycardia after myocardial infarction. *Circulation* 1981;**64**:235–42.

26 Buckingham TA, Thessen CC, Stevens LL, Redd RM, Kennedy HL. Effect of conduction defects on the signal-averaged electrocardiographic determination of late potentials. *Am J Cardiol* 1988;**61**:1265–71.

27 Nie NH, Hull CH, Jenkins JG, Steinbrenner K, Bent DH. *Statistical package for the social sciences.* 2nd ed. New York: McGraw-Hill, 1974:1–467

28 Henning H, Gilpin EA, Covell JW, Swann EA, Orourke RA, Ross J. Prognosis after acute myocardial infarction: a multivariate analysis of mortality and survival. *Circulation* 1979;59:1124–36.

29 Bay KS, Lee SJK, Flathman DP, Roll JW, Piercy W. Application of step-wise discriminant analysis and Bayesian classification procedure in determining prognosis of acute myocardial infarction. *Can Med Assoc J* 1976;**115**:887–92.

30 Hsu L, Senaratne MPJ, Desilva S, Rossall RE, Kappagoda T. Prediction of coronary events following myocardial infarction using a discriminant function analysis. *J Chronic Dis* 1986;**39**:543–52.

31 Muller JE, Ludmer PL, Willich SN, *et al.* Circadian variation in the frequency of sudden cardiac death. *Circulation* 1987;**75**:131–8.

32 Nicod P, Gilpin E, Dittrich H, *et al.* Late clinical outcome in patients with early ventricular fibrillation after myocardial infarction. *J Am Coll Cardiol* 1988;**11**:464–70.

33 Tofler GH, Stone PH, Muller JE, *et al.* Prognosis after cardiac arrest due to ventricular tachycardia or ventricular fibrillation associated with acute myocardial infarction (the MILIS study). *Am J Cardiol* 1987;**60**:755–61.

34 Lawrie DM. Long-term survival after ventricular fibrillation complicating acute myocardial infarction. *Lancet* 1969;**ii**:1085–7.

35 Boudoulas H, Sohn Y, Brown R, Weissler AM. Left ventricular dysfunction is a determinant of improved survival with beta-blockade therapy following myocardial infarction. *IRCS Med Sci* 1985;**13**:271–2

36 Brubakk O, Pedersen TR, Overskeid K. Noninvasive evaluation of the effect of timolol on left ventricular performance after myocardial infarction and the

consequence for prognosis. *J Am Coll Cardiol* 1987;9:155–60

37 Weissler AM. The systolic time intervals and risk stratification after acute myocardial infarction. *J Am Coll Cardiol* 1987;9.161–2.

38 Weissler AM, O'Neill WW, Sohn YH, Stack RS, Chew PC, Reed AH. The prognostic significance of systolic time intervals after recovery from myocardial infarction. *Am J Cardiol* 1981;**48**:995–1002.

39 Eagle KA, Quertermous T, Singer DE, *et al.* Left ventricular ejection fraction. Physical estimates compared with gated blood pool scan measurements. *Arch Intern Med* 1988;**148**·882–5.

40 Battler A, Karliner JS, Higgins CB, *et al.* The initial chest *x* ray in acute myocardial infarction. Prediction of early and late mortality and survival. *Circulation* 1980;**61**:1004–9.

41 Battler A, Slutsky R, Karliner J, Froelicher V, Ashburn W, Ross J. Left ventricular ejection fraction and first third ejection fraction early after acute myocardial infarction: value for predicting mortality and morbidity. *Am J Cardiol* 1980;**45**:197–202.

42 Wolffenbuttel BHR, Verdouw PD, Scheffer MG, Bom HPA, Bijleveld RE, Hugenholtz PG. Significance of haemodynamic variables in coronary care unit for prediction of survival after acute myocardial infarction. *Br Heart J* 1983;**50**:266–72.

43 Dwyer EM, Greenberg H, Case RB Association between transient pulmonary congestion during acute myocardial infarction and high incidence of death in six months. *Am J Cardiol* 1986;**58**:900–5.

44 Greenberg H, McMaster P, Dwyer EM. Left ventricular dysfunction after acute myocardial infarction: results of a prospective multicenter study. *J Am Coll Cardiol* 1984;**4**:867–74.

45 Warnowicz MA, Parker H, Cheitlin MD Prognosis of patients with acute pulmonary edema and normal ejection fraction after acute myocardial infarction. *Circulation* 1983;**67**:330–4.

46 Nicod P, Gilpin E, Dittrich H, *et al.* Influence on prognosis and morbidity of left ventricular ejection fraction with and without signs of left ventricular failure after acute myocardial infarction. *Am J Cardiol* 1988;**61**:1165–71.

47 Stewart DE, Ikram H, Espiner EA, Nicholls MG. Arrhythmogenic potential of diuretic induced hypokalaemia in patients with mild hypertension and ischaemic heart disease. *Br Heart J* 1985;**54**:290–7.

48 Schelbert HR, Henning H, Ashburn WL, Verba JW, Karliner JS, Orourke RA. Serial measurements of left ventricular ejection fraction by radionuclide angiography early and late after myocardial infarction. *Am J Cardiol* 1976;**38**:407–15.

49 Sniderman AD, Beaudry JP, Rahal DP. Early recognition of the patient at late high risk: incomplete infarction and vulnerable myocardium. *Am J Cardiol* 1983;**52**:669–73.

50 Schwartz H, Leiboff RL, Katz RJ, *et al.* Arteriographic predictors of spontaneous improvements in left ventricular function after myocardial infarction. *Circulation* 1985;**71**:466–72.

51 Fioretti P, Brower RW, Simoons ML, *et al.* Relative value of clinical variables, bicycle ergometry, rest radionuclide ventriculography and 24 hour ambulatory electrocardiographic monitoring at discharge to predict 1 year survival after myocardial infarction. *J Am Coll Cardiol* 1986;**8**:40–9.

52 Fioretti P, Brower RW, Lazzeroni E, *et al.* Limitations of a QRS scoring system to assess left ventricular function and prognosis at hospital discharge after myocardial infarction. *Br Heart J* 1985;**53**:248–52.

53 Winkle RA, Peters F, Hall R Characterization of ventricular tachyarrhythmias on ambulatory ECG recordings in post-myocardial infarction patients. arrhythmia detection and duration of recording, relationship between arrhythmia frequency and complexity, and day-to-day reproducibility. *Am Heart J* 1981;**102**.162–9.

54 Maisel AS, Scott N, Gilpin E, *et al.* Complex ventricular arrhythmias in patients with Q wave versus non-Q wave myocardial infarction. *Circulation* 1985;**72**:963–70.

55 Olson HG, Lyons KP, Troop P, Butman SM, Piters KM. Prognostic implications of complicated ventricular arrhythmias early after hospital discharge in acute myocardial infarction: a serial ambulatory electrocardiography study. *Am Heart J* 1984; **108**·1221–8.

56 Kostis JB, Byington R, Friedman LM, Goldstein S, Furberg C Prognostic significance of ventricular ectopic activity in survivors of acute myocardial infarction. *J Am Coll Cardiol* 1987;**10**:231–42.

57 Bigger JT, Weld FM, Rolnitzky LM. Prevalence, characteristics and significance of ventricular tachycardia (three or more complexes) detected with ambulatory electrocardiographic recording in the late hospital phase of acute myocardial infarction. *Am J Cardiol* 1981;**48**:815–23.

58 Davis HT, Decamilla J, Bayer LW, Moss AJ. Survivorship patterns in the posthospital phase of myocardial infarction. *Circulation* 1979;**60**:1252–8.

59 Schulze RA, Strauss HW, Pitt B. Sudden death in the year following myocardial infarction. Relation to ventricular premature contractions in the late hospital phase and left ventricular ejection fraction. *Am J Med* 1977;**62** 192–9.

60 Bigger JT, Fleiss JL, Rolnitzky LM. Prevalence, characteristics and significance of ventricular tachycardia detected by 24-hour continuous electrocardiographic recordings in the late hospital phase of acute myocardial infarction. *Am J Cardiol* 1986;**58**:1151–60.

61 Mukharji J, Rude RE, Poole WK, *et al.* Risk factors for sudden death after acute myocardial infarction: two year follow-up. *Am J Cardiol* 1984;**54**.31–6.

62 Multicenter Postinfarction Research Group. Risk stratification and survival after myocardial infarction. *N Engl J Med* 1983;**309**:331–6.

63 Rapaport E, Remedios P. The high risk patient after recovery from myocardial infarction: recognition and management. *J Am Coll Cardiol* 1983;**1**.391–400.

64 Smith JW, Marcus FI, Serokman R. Prognosis of patients with diabetes mellitus after acute myocardial infarction. *Am J Cardiol* 1984;**54**:718–21.

Br Heart J 1989;62:438–44

A comparison of methods of analysing exercise tests for diagnosis of coronary artery disease

JAAP W DECKERS, BENNO J RENSING, JAN G P TIJSSEN, RUUD V H VINKE, AIDA J AZAR, MAARTEN L SIMOONS

From the Thoraxcenter, Division of Cardiology, Academic Hospital Rotterdam "Dijkzigt" and Erasmus University, Rotterdam, The Netherlands

SUMMARY The diagnostic accuracy of the following methods of analysing exercise tests were evaluated: (*a*) the cumulative area of ST segment depression during exercise normalised for workload and heart rate (exercise score); (*b*) discriminant analysis of electrocardiographic exercise variables, workload, and symptoms; and (*c*) ST segment amplitude changes during exercise adjusted for heart rate. Three hundred and forty five men without a history of myocardial infarction were studied. One hundred and twenty three were apparently healthy. Less than half (170) had coronary artery disease. All had a normal electrocardiogram at rest. A Frank lead electrocardiogram was computer processed during symptom limited bicycle ergometry. The accuracy of the exercise score (*a*) was low (sensitivity 67%, specificity 90%). Discriminant analysis (*b*) and ST segment amplitude changes adjusted for heart rate (*c*) had excellent diagnostic characteristics (sensitivity 80%, specificity 90%), which were little affected by concomitant use of β blockers. Both methods seem well suited for diagnostic application in clinical practice.

In 1977 a system for computer assisted interpretation of exercise electrocardiograms was introduced in our hospital. This system used ST segment amplitudes and ST segment slopes adjusted for heart rate, and was more accurate than visual interpretation of the exercise electrocardiogram.[1] Since then, various other complex diagnostic analyses have been described that include not only electrocardiographic variables but also other exercise variables.[2-4] Hollenberg *et al* proposed a treadmill exercise score that measures the cumulative area of ST segment depression during exercise normalised for workload.[2 5] In 116 men with a high likelihood of coronary disease this score had a sensitivity of 85% and a specificity of 91%.[2] Among 45 men with a low likelihood of coronary disease but with a positive test according to conventional interpretation, the score identified the one who had coronary artery disease and produced no false positive responses.[5] Detry *et al* developed a discriminant function that correctly classified 83% of a study population of 370 men without previous myocardial infarction.[3] Detrano *et al* recently assessed the relative value of ST segment slope, R wave amplitude, and ST amplitude adjusted for heart rate and R wave amplitude in 303 patients without previous infarction and concluded that simple adjustment of ST segment changes for exercise induced heart rate gave the best diagnostic accuracy.[4] Claims that these techniques enhance the diagnostic accuracy of exercise electrocardiography have not yet been confirmed in an independent series of patients. We examined the merits of these approaches in men without a previous myocardial infarction.

Patients and methods

STUDY POPULATION

We studied 345 men. None of them had a prior myocardial infarction or was taking digitalis. All had a normal electrocardiogram at rest. The study group included 222 men consecutively referred between January 1978 and May 1983 for evaluation of chest pain, who performed a symptom limited exercise test and subsequently underwent coronary angiography. Symptoms were classified according to the criteria of the Coronary Artery Surgery Study register.[6] Left ventriculography and coronary angiography were

Requests for reprints to Dr Jaap W Deckers, Thoraxcenter, Bd 381, University Hospital "Dijkzigt", Dr Molewaterplein 40, 3015 GD Rotterdam, The Netherlands

Accepted for publication 14 June 1989

Table 1 *Electrocardiographic and exercise variables of the various diagnostic exercise analyses*

Analysis	*ST amplitude*	*ST slope*	*R wave*	*HR*	*Workload*	*Angina*
HR adjusted ST and slope[1]	ST_{20}, ST_{80} (X)	ST_{20-80} (X)		+		
Exercise score[2 3]	J point (X and Y)	ST_{20-60} (X and Y)	+	+	+	
Discriminant function[4]	ST_{60} (X)	ST_{20-60} (X)		+	+	+
HR adjusted ST amplitudes[5]	ST_{80} ex-ST_{80} rest (X)			+		

HR, heart rate; ex, peak exercise.
ST_{20}, ST segment amplitudes at 20 ms after J.
X and Y, Frank leads X and Y.

performed within three months of the exercise test. The presence of a diameter stenosis of at least 50% in one or more major coronary arteries was regarded as evidence of coronary disease. Angiograms were interpreted by two experienced cardiologists without knowledge of the exercise test results. Ninety five patients with coronary disease and 21 patients with normal angiograms were taking β blockers at the time of the exercise test.

The other 123 men were studied in the Kaunas-Rotterdam Intervention Study. In this World Health Organisation project, a representative sample of men in Rotterdam was screened for the presence of coronary risk factors.[7] A subgroup volunteered to participate in the exercise study. They were without symptoms and none of them was taking cardiac medication.

EXERCISE TEST

The men performed a symptom limited exercise test while sitting on a bicycle ergometer. The workload was increased by 10 or 20 W until moderate symptoms appeared or until exhaustion occurred. The men continued to cycle at a low load for four minutes after peak exercise. The corrected orthogonal Frank lead electrocardiogram was recorded with the chest electrodes attached at the level of the fifth intercostal space. The electrocardiogram was computer processed as described elsewhere.[8] In short, the electrocardiogram was sampled for 20 seconds with the man sitting at rest, every minute during exercise, and during a six minute recovery period. The sampling frequency was 250 Hz. After rejection of abnormal complexes or those showing excessive baseline drift, an average representative complex was calculated.[9] The baseline level was defined as the mean signal amplitude for 5–3 samples (20–12 ms) before the QRS complex. All amplitudes were measured relative to this baseline. Measurements included heart rate, R wave amplitude, J point amplitude, and ST segment amplitudes every 20 ms intervals between the J point and 100 ms after J in leads X and Y. ST_{20} is the ST amplitude 20 ms after J.

The following diagnostic analyses, outlined in table 1, were evaluated:

(*a*) ST segment measurements adjusted for instantaneous heart rate.[1] The diagnostic accuracy of the combination of ST_{20} and ST_{80} in Frank lead X, corrected for heart rate, was re-evaluated.

(*b*) A modification of the treadmill exercise score as described by Hollenberg *et al.* This score quantifies the electrocardiographic response to exercise by measuring the cumulative area of ST segment amplitude during exercise and recovery in leads V5 and aVF, which is then normalised for QRS amplitude and for workload—by dividing the ST segment sum by the product of the duration of exercise (in minutes) and the fraction of the maximal

Table 2 *Results of discriminant analysis of exercise variables in 345 men without previous myocardial infarction for coefficients derived by Detry et al[3] and for those obtained in the present study*

	Detry et al[3]			*This study*		
		*Discriminant score**			*Discriminant score**	
Exercise variables	*Coefficient*	*CAD*	*Normal*	*Coefficient*	*CAD*	*Normal*
Heart rate (beats/min)	0·02	2·79	3·55	0·02	2·28	3·00
ST_{60} lead X (mV)	3·78	−0·53	−0·11	7·00	−0·78	0·21
Angina (yes: 1, no 2)	0·78	1·09	1·56	0·92	1·28	1·53
Workload (W)	0·004	0·59	0·90	0·004	0·46	0·67
ST_{20-60} slope lead X (mV/s)	0·16	0·10	0·44	0·21	0·09	0·46
Intercept	−5·04	−5·04	−5·04	−4·38	−4·38	−4·38
Overall discriminant score†		−1·00	1·30		−1·05	1·49

CAD, coronary artery disease.
*Calculated as the product of the coefficient and the mean value of the variable.
†Calculated as the sum of the item-specific scores; this score can be regarded as the discriminant score of the average patient.

predicted heart rate (MPHR) achieved.[2 5 10] We modified the original method by using Frank leads X and Y instead of standard leads V5 and aVF and by limiting the electrocardiographic measurements in the recovery period to six minutes after peak exercise instead of 10 minutes. The ST segment slope was calculated from ST segment amplitudes at 20 and 60 ms, because this was the most informative slope in our study population. The slope measurements in the original publication were not specified. The maximal predicted heart rate (MPHR) was calculated 220 − age. Mean R wave amplitude values obtained in the present study population were entered as R in the formula:

$$\begin{aligned}&\text{Exercise score} = \text{area (J point + ST slope) lead X}\\ &\times \bar{R}/\text{R lead X} + \text{area (J point + ST slope) lead Y}\\ &\times \bar{R}/\text{R lead Y} - \text{exercise duration} \times \text{fraction of MPHR}\end{aligned}$$

(*c*) The discriminant function (D) described by Detry *et al* and presented in table 2.[3]

(*d*) The electrocardiographic method of Detrano *et al*.[4] Changes in ST amplitude were adjusted for heart rate in Frank lead X only:

$$\begin{aligned}&(\text{ST}_{80}\text{ exercise} - \text{ST}_{80}\text{ rest) lead X} - \text{heart rate adjusted ST}\\ &= \text{exercise heart rate} - \text{resting heart rate}\end{aligned}$$

STATISTICAL ANALYSIS

We used univariate analysis with unpaired Student's *t* test for continuous variables and Fisher's exact test for discrete variables. Stepwise discriminant analysis was performed with the BMDP 7M statistical package. The sensitivity and specificity of the various electrocardiographic variables and of the different diagnostic analyses and their sub-elements were presented as receiver operator characteristic curves (sensitivity *v* specificity).[11 12]

Table 3 *Clinical and angiographic data of 345 men without previous myocardial infarction*

History	*No*	*Age (yr) Mean*	*Range*	*CAD No (%)*
Typical angina	124	52	28–69	111 (90)
Atypical angina	63	50	30–66	43 (68)
Non-anginal pain	35	46	22–68	16 (46)
Volunteers	123	47	19–64	— —

CAD, coronary artery disease.

Results

Table 3 shows the details of the study population. Of the 170 patients with coronary disease, one had left main disease, 53 had three vessel disease, 64 two vessel disease, and 52 single vessel disease. The mean ejection fraction of the patients with coronary disease was 64% (range 37–83). The other 52 men with symptoms had normal coronary arteries or no significant lesions at angiography. Angiography was not performed in the 123 men without symptoms. A follow up of 9 years (SD 9 months) confirmed that they did not have heart disease. Six of them had died; whereas the number of deaths expected in a random sample of Dutch men of similar age would have been 12.[13]

No complications occurred during exercise testing. Table 4 shows the relevant exercise variables. Patients with coronary disease reached lower maximal workload and lower peak heart rate and ST segment amplitudes in leads X and Y were significantly more negative than in the other men. Patients with normal angiograms had intermediate mean exercise values, although their individual electrocardiographic variables fell within the ranges of the healthy subjects.

Table 4 *Exercise test data in 170 patients with coronary disease (CAD), in 52 patients with normal coronary angiograms (No CAD), and in 123 symptom free men. Measurements are given at peak exercise unless otherwise indicated. All data, except angina, are given as mean (SD)*

	CAD (n = 170)		*No CAD and healthy men (n = 175)*		*No CAD (n = 52)*		*Healthy men (n = 123)*	
Max workload (W)	115	(33)**	168	(43)	156	(46)*	173	(41)
Angina (%)	103	(61)**	7	(4)	7	(13)	—	
Max heart rate (beats/min)	120	(22)**	158	(24)	143	(28)*	165	(18)
R wave lead X at rest (μV)	1304	(423)	1369	(451)	1358	(483)	1374	(439)
ST_{60} lead X (μV)	−112	(79)**	30	(92)	−7	(62)*	44	(97)
ST_{80} lead X (μV)	−92	(100)**	117	(139)	45	(92)*	144	(144)
ST_{20-60} slope lead X (μV/s)	0 43	(0 93)**	2 16	(1 37)	1 54	(0·94)*	2 41	(1·44)
R wave lead Y at rest (μV)	547	(328)	654	(396)	681	(416)	643	(389)
ST_{60} lead Y (μV)	−46	(63)**	10	(66)	−16	(55)*	21	(67)
ST_{80} lead Y (μV)	−31	(76)**	51	(92)	2	(69)*	70	(92)
ST_{20-60} slope lead Y (μV/s)	0 43	(0 62)**	1·28	(0 84)	0 97	(0 70)	1·40	(0 87)

*p = < 0 02 No CAD *v* healthy men.
**p = < 0 001 CAD *v* all men with normal tests.

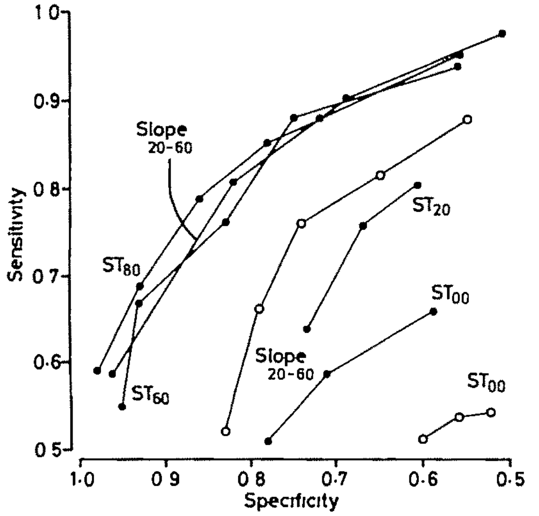


Fig 1 *Sensitivity and specificity for the prediction of coronary disease of ST_{00} in Frank leads X (solid circles) and Y (open circles), ST_{20}, ST_{60}, and ST_{80} in lead X, and ST_{20-60} slope in leads X and Y in 345 men without previous myocardial infarction.*

ST_{60} and ST_{80} in lead X had a sensitivity of 70% and a specificity of 90% for the prediction of coronary disease. The ST_{20-60} slope in lead X had similar diagnostic value (fig 1). The diagnostic accuracy of ST_{20} was lower, while values for ST segment measurements at 40 and 100 ms in lead X were intermediate (not illustrated). Other electrocardiographic variables used in the various formulas, such as J point amplitudes in leads X and Y and ST_{20-60} slope in lead Y were inaccurate indicators for the presence or absence of coronary disease (fig 1).

The diagnostic yield of ST segment measurements adjusted for instantaneous heart rate was good (sensitivity 74%, specificity 90%) in the study population as a whole (fig 2, table 5). These measurements, however, were less reliable in the 116 men who were treated with β blockers (95 men with coronary disease and 21 men with normal angiograms) (table 5).

The diagnostic accuracy of the exercise score was low, even in patients not taking β blockers (fig 2, table 5). Conventional ST segment measurements in lead X were more powerful predictors. To determine the strong and weak components of the exercise score, the various elements of the original formula were analysed. When only the numerator of the equation, the cumulative J point depression and ST segment slope, was evaluated the test's accuracy increased. In contrast, addition of the maximum predicted heart rate or achieved workload to the denominator of the equation reduced the diagnostic value of the test (table 5).

The sensitivity and specificity of the discriminant function developed and described by Detry *et al*[3] were quite high (fig 2). This analysis also proved to be accurate in patients taking β blockers, although the sensitivity was higher at corresponding levels of specificity in patients who were not taking these drugs (table 5). The coefficients of the discriminant function in this series of patients were calculated by stepwise discriminant analysis with the same variables as used by Detry *et al.* Table 2 shows the derived coefficients and table 5 the sensitivity and specificity of this analysis. ST segment amplitude was more important in this "optimised" equation, and the differences between the coefficients of the two discriminant functions related to ST_{60} were statistically significant.

The sensitivity of the ST segment changes adjusted for heart rate was high at all levels of specificity (fig 2, table 5). The results of the analysis were not affected by the use of β blocking agents during exercise. The sensitivity and specificity of the test were poor when the unadjusted difference between ST segment measurements at peak exercise and at rest were evaluated. The subsequent correction of the ST segment changes for R wave amplitude only improved this component of the test's yield at high levels of specificity (table 5).

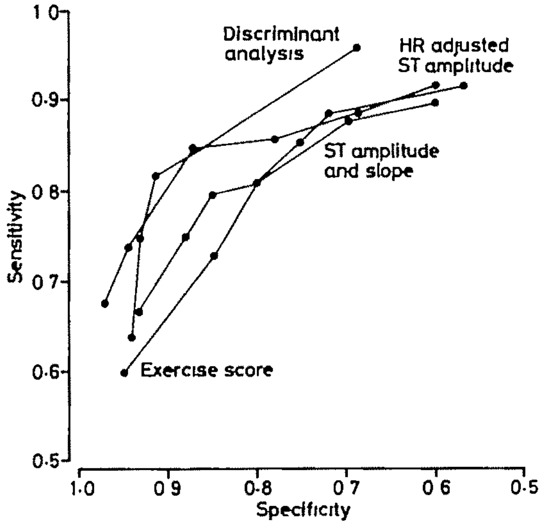


Fig 2 *Sensitivity and specificity for the prediction of coronary disease of changes in ST segment adjusted for instantaneous heart rate,*[1] *of exercise score,*[2 5] *and of discriminant function according to Detry et al*[3] *and of changes in ST amplitude adjusted for heart rate as proposed by Detrano et al*[4] *in 345 men.*

Table 5 *Sensitivities (%) at fixed specificity for various diagnostic analyses of exercise tests and their components*

	Specificity (%)			
	80	*85*	*90*	*95*
HR adjusted ST amplitudes and slope[1]:				
All patients	82	79	74	58
Patients with β blockers	73	64	63	43
Patients without β blockers	84	81	76	68
Exercise score[2 5]:				
All patients	82	73	67	60
Patients with β blockers	74	68	66	58
Patients without β blockers	78	70	63	53
ST area measurements only	91	84	71	55
Area/% MPHR	68	61	44	29
Area/minutes in test	77	67	56	40
Discriminant function according to Detry *et al*[3]				
All patients	88	86	84	50
Patients with β blockers	89	82	71	66
Patients without β blockers	91	89	84	54
Present discriminant analysis	95	92	91	78
HR adjusted ST segment changes[4]:				
All patients	84	82	78	73
Patients with β blockers	81	81	80	77
Patients without β blockers	81	78	76	64
ST$_{80}$ max—ST$_{80}$ rest	80	73	65	56
Correction for R wave amplitude	80	73	70	61

HR, heart rate; MPHR, maximum predicted heart rate

Discussion

The success of apparently promising new diagnostic techniques is often found to be limited when they are applied to other populations.[14] Inappropriate selection of patients and biased evaluation of the test and disease state are the usual causes of such failures[15]; the contribution of different stress test protocols or electrocardiographic techniques is less crucial.[16] We studied patients with a broad range of coronary disease: men without coronary disease who were apparently very healthy, and men with symptoms who did not have important coronary disease. Figure 3 shows that the results of the exercise test were related to the severity of coronary disease.

Discriminant function analysis of exercise variables and ST segment amplitude changes adjusted for heart rate seemed to be the best predictors of the absence or presence of obstructive coronary disease. Both analyses had a sensitivity between 70% and 80% at a specificity level of 90%. The diagnostic accuracy was highest with the discriminant function according to Detry *et al.*[3] The coefficients obtained in the present study resembled the original values reported by Detry *et al*[3] although the weight given to ST segment changes in our equation was higher. The relative importance of the various exercise variables in the discriminant analyses became apparent when the mean exercise variables of the two patient groups were entered in the two equations (table 2). Heart rate at peak exercise, ST$_{60}$ in lead X, and the appearance of angina during exercise were the most important variables, as they were in other studies.[17–19] Although exercise tolerance is a major indicator of prognosis in patients with known coronary disease,[20] workload was not an important factor in the diagnosis of coronary disease by either function in patients without a previous myocardial infarction and normal left ventricular function. The use of anginal symptoms during exercise in the discriminant function may not be appropriate because bayesian probability analysis relies on the mutual independence of variables; angina may have already been used to calculate the pre-test risk of coronary disease.[21]

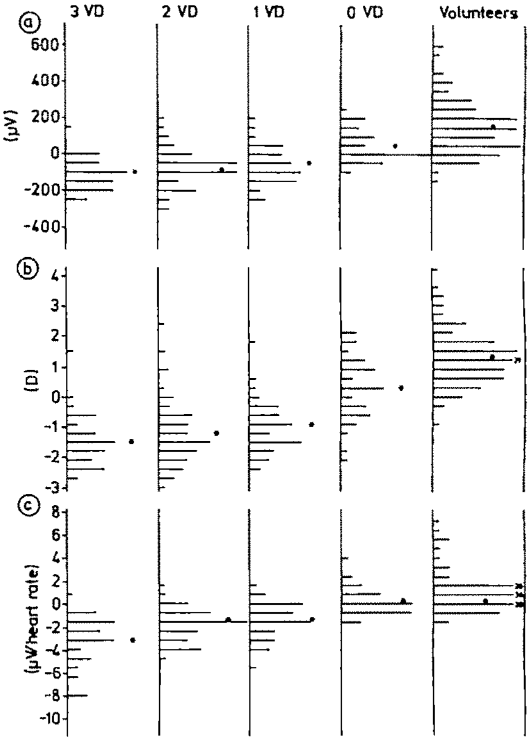


Fig 3 *Exercise variables ST$_{80}$ in lead X for values obtained with the discriminant function according to Detry et al[3] and for ST segment amplitudes adjusted for heart rate in 345 men with three vessel disease (VD), two vessel disease, single vessel disease, patients with normal findings at angiography (No CAD), and volunteers. (a) Distribution of ST$_{80}$. (b) Discriminant function according to Detry et al.[3] (c) ST segment amplitude adjusted for heart rate. A complete column represents 20 subjects. The asterisk indicates the mean in that group. Note the overlap between the various groups, in particular between 1 VD and 2 VD. Patients with three vessel disease showed the most abnormal results and volunteers the most normal results.*

The adjustment of ST segment amplitude for heart rate in the manner proposed by Detrano *et al*[4] yielded similar diagnostic results—a sensitivity of 78% at a specificity level of 90%. This is remarkable because we evaluated ST segment changes in Frank lead X only. The processing of the electrocardiographic variables by computer and the exclusion of data from women in this study probably account for this excellent result.[22 23]

Surprisingly, the method with the lowest diagnostic accuracy was the exercise score. But in theory some features of this score are appealing. Its use of the cumulated changes in J point and ST segment slope during the full test period seems to be attractive, because this will reduce errors inherent in single measurements at peak exercise. On the other hand, the test score was adversely affected when there was low exercise capacity not caused by cardiac factors or when other disorders precluded normal exercise capacity. Such conditions are common in middle aged patients with symptoms and to some extent could explain the relatively poor performance of the exercise score in this study. In addition, exercise capacity, which was a relatively unimportant variable in the discriminant analyses, was included in the exercise score. Also, the J point amplitude in the numerator of the equation was not the most accurate of the various electrocardiographic variables studied. The results of another study in which ST segment measurements were taken at 80 ms after J instead of at the J point were also disappointing.[24] There were important differences between the exercise score in this study and its original description by Hollenberg *et al.* Although the tests in both studies were symptom limited and the workload was increased in stages in both, the two methods cannot be directly compared; we used bicycle ergometry and they used a treadmill.

Earlier, we reported a sensitivity of 84% and a specificity of 88% when ST measurements at 20 and 80 ms and instantaneous heart rates in Frank lead X were combined. In the current population, the diagnostic accuracy of the method was lower (sensitivity 74%, specificity 90%): in addition, the usefulness of the method was strongly influenced by the use of β blockers during exercise, which makes it less reliable than the other methods tested.

In the current comparison of various diagnostic approaches to exercise tests in men with a normal electrocardiogram at rest, the most complex technique considered, the discriminant function as described by Detry *et al*, was the most accurate. The simplest analysis, the adjustment of the ST segment amplitude changes for heart rate, came second. Neither method was affected by the use of β blockers during exercise. Because the workload contributes little to the strength of the discriminant analysis, both techniques rely most on the same haemodynamic and electrocardiographic variables—heart rate and ST segment depression. These variables were also associated with the presence or absence of coronary disease in other studies, even when clinical variables were taken into account.[25] Thus discriminant analysis and ST segment changes adjusted for heart rate are both good methods for the diagnosis or exclusion of coronary artery disease in men. When computer facilities are not available, measurement of ST amplitude adjusted for heart rate is the most appropriate choice of analysis.

References

1 Simoons ML, Hugenholtz PG. Estimation of the probability of exercise-induced ischemia by quantitative ECG analysis. *Circulation* 1977;56:552–9.

2 Hollenberg M, Budge WR, Wisneski JA, Gertz EW. Treadmill score quantifies electrocardiographic response to exercise and improves test accuracy and reproducibility. *Circulation* 1980;61:276–85.

3 Detry JMR, Robert A, Luwaert RJ, *et al.* Diagnostic value of computerized exercise testing in men without previous myocardial infarction. A multivariate, compartmental and probabilistic approach. *Eur Heart J* 1985;6:227–38.

4 Detrano R, Salcedo E, Passalacqua M, Friis R. Exercise electrocardiographic variables: a critical appraisal. *J Am Coll Cardiol* 1986;4:836–47.

5 Hollenberg M, Zoltick JM, Go M, *et al.* Comparison of a quantitative treadmill exercise score with standard electrocardiographic criteria in screening asymptomatic young men for coronary artery disease. *N Engl J Med* 1985;313:600–6.

6 Chaitman BR, Bourassa MG, Davis K, *et al.* Angiographic prevalence of high-risk coronary artery disease in patient subsets (CASS). *Circulation* 1981;64:360–7.

7 Simoons ML. Computer assisted interpretation of exercise electrocardiograms. Rotterdam: Erasmus University, 1976. Thesis.

8 Simoons ML, Boom HBK, Smallburg E. On-line processing of orthogonal exercise electrocardiograms. *Comput Biomed Res* 1975;8:105–17.

9 Van Bemmel JH, Talmon JL, Duisterhout JS, Hengeveld SJ. Template waveform recognition applied to ECG/VCG analysis. *Comput Biomed Res* 1973;6:430–41.

10 Hollenberg M, Go M, Massie BM, Wisneski JA, Gertz EW. Influence of R-wave amplitude on exercise-induced·ST depression: need for a "gain factor" correction when interpreting stress electrocardiograms. *Am J Cardiol* 1985;56:13–7.

11 McNeil BJ, Keeler E, Adelstein SJ. Primer of certain elements on medical decision making. *N Engl J Med* 1975;293:211–5.

12 Swets JA. Measuring the accuracy of diagnostic systems. *Science* 1988;240:1285–93.

13 Maandstatistiek van de Bevolking. Centraal Bureau

voor Statistiek, 's-Gravenhage 1982;**30**:43–4.

14 Rozanski A, Diamond GA, Berman D, Forrester JS, Morris D, Swan HJC. The declining specificity of exercise radionuclide ventriculography. *N Engl J Med* 1983;**309**:518–22.

15 Ransohoff DF, Feinstein AR. Problems of spectrum and bias in evaluating the efficacy of diagnostic tests. *N Engl J Med* 1978;**299**:926–30.

16 Philbrick JT, Horwitz RI, Feinstein AR. Methodologic problems of exercise testing for coronary artery disease: groups, analysis and bias. *Am J Cardiol* 1980;**46**:807–12.

17 Berman JL, Wynne J, Cohn PF. A multivariate approach for interpreting treadmill exercise tests in coronary artery disease. *Circulation* 1978;**58**:505–12.

18 Greenberg PS, Ellestad MH, Clover RC. Comparison of the multivariate analysis and CADENZA systems for determination of the probability of coronary artery disease. *Am J Cardiol* 1984;**53**:493–6.

19 Hung J, Chaitman BR, Lam JL, *et al.* A logistic regression analysis of multiple noninvasive tests for the prediction of the presence and extent of coronary artery disease in men. *Am Heart J* 1985;**110**:460–9.

20 Krone RJ, Gillespie JA, Weld FM, Miller JP, Moss AJ, and the Multicenter Postinfarction Research Group. Low-level exercise testing after myocardial infarction: usefulness in enhancing clinical risk stratification. *Circulation* 1985;**71**:80–9.

21 Weintraub WS, Madeira SW, Bodenheimer MM, *et al.* Critical analysis of the application of Bayes' theorem to sequential testing in the noninvasive diagnosis of coronary artery disease. *Am J Cardiol* 1984;**54**:43–9.

22 Bhargava V, Watanabe K, Froelicher VF. Progress in computer analysis of the exercise electrocardiogram. *Am J Cardiol* 1981;**47**:1143–51.

23 Barolsky SM, Gilbert CA, Faruqui A, Nutter DO, Schlant RC. Differences in electrocardiographic response to exercise of women and men: a non-bayesian factor. *Circulation* 1979;**60**:1021–7.

24 Vergari J, Hakki AH, Heo J, Iskandrian AS. Merits and limitations of quantitative treadmill exercise score. *Am Heart J* 1987;**114**:819–26.

25 Fisher LD, Kennedy JW, Chaitman BR, *et al.* Diagnostic quantification of CASS (Coronary Artery Surgery Study) clinical and exercise test results in determining presence and extent of coronary artery disease. A multivariate approach. *Circulation* 1981;**63**:987–1000.

Br Heart J 1989;62:445–9

Physiological hypertrophy of the heart and atrial natriuretic peptide during rest and exercise

JENS SVANEGAARD,* KRISTIAN ANGELO-NIELSEN, JAN SCHULTZ HANSEN

*From the Department of *Clinical Chemistry and the Department of Cardiology and Internal Medicine, Svendborg Hospital, Svendborg, Denmark*

SUMMARY The influence of physiological cardiac hypertrophy on the concentration of plasma atrial natriuretic peptide was studied in six male athletes and six normally active, matched control men. They were examined by echocardiography during a graded exercise test on a bicycle ergometer. Plasma atrial natriuretic peptide was measured at rest, at each workload until exhaustion, and 15 and 30 minutes after the exercise test. Echocardiography showed that the athletes had a significantly larger left atrium, left ventricular end diastolic diameter, left ventricular posterior wall, interventricular septum, left ventricular ejection fraction, and left ventricular mass than the controls. The athletes performed significantly more work than the control group—325 W *v* 277 W. The plasma concentration of atrial natriuretic peptide rose by a mean factor of 2·76 (range 1·78–4·28) in all men from rest to maximum exercise. There were no differences between the athletes and the controls in the concentrations of plasma atrial natriuretic peptide at rest, at any workload, or at maximum workload. Neither was there any difference in the increase in plasma atrial natriuretic peptide between the groups. There was no correlation between the plasma concentrations of atrial natriuretic peptide and any of the variables measured by echocardiography.

In healthy young men plasma atrial natriuretic peptide rises by a factor of about 2·8 during maximum exercise and the size of the chambers on the left side of the heart or left ventricular hypertrophy does not seem to influence the concentration of plasma atrial natriuretic peptide at rest or during exercise.

Atrial natriuretic peptide is a circulating hormone secreted by the atrial myocytes of the heart. It is released in response to increased atrial pressure,[1] which is generally equal to increased stretch and dilatation of the atrial wall. Plasma atrial natriuretic peptide rose during exercise.[2]

The term "athelete's heart" was introduced by Henschen in 1899.[3] In this condition all the chambers of the heart are dilated and there is hypertrophy of the myocardium due to physical training.[4 5]

The purpose of this study was to determine whether the hypertrophy and dilatation of the heart seen in well trained persons influence the plasma concentration of atrial natriuretic peptide at rest or during exercise.

Patients and methods

We studied six male footballers who trained strenuously and six normally active healthy matched controls (aged 21–30 years). None was taking medical treatment. The controls did not participate in any form of athletics for more than four hours a week. They all gave informed consent and the study was approved by the local ethics committee.

All of the investigations were undertaken between 3 pm and 7 pm. Echocardiography, with cross sectional and M mode recordings, was performed with a Hewlett Packard 77020A ultrasonograph and a 3·5 MHz transducer on men in the supine position. All the M mode measurements originated from three or four consecutive cardiac cycles graded according to the system of the American Society of Echocardiography.[6] Calculations of the left ventricular ejection fraction and the left ventricular mass were based on the assumption that the left ventricle is ellipsoid.[7] We took Henry *et al's* data as normal values,[8] except

Requests for reprints to Dr Jens Svanegaard, Department of Cardiology, Odense University Hospital, Odense C, Denmark DK-5000.

Accepted for publication 27 June 1989

for the calculation of the left ventricular mass, where we used the formula: left ventricular mass $= 43.62 + 2.18 \times$ weight(kg). The upper normal limit was +2 standard deviations (that is the left ventricular mass plus 30%).[9]

The men had fasted for two hours before the exercise test and a cannula was inserted in an antecubital vein 30 minutes before the test. An electrocardiogram and auscultation of the heart were obtained before the test.

The subjects sat on the bicycle ergometer after a 30 minute rest in the supine position then blood pressure and pulse rate were measured. Graded exercise was performed by increasing the workload by 60 W every three minutes, starting at 120 W and continuing until exhaustion. Blood pressure and pulse rate were measured and a blood sample was drawn during the last 60 seconds of each work period and at 15 and 30 minutes after maximum exercise with the subject resting on the bicycle or a chair. Blood pressure was measured by the standard cuff technique.

Samples were collected in tubes coated in edetic acid and containing aprotinin (500 IU/ml blood) and kept in an ice bath. After centrifugation for 15 minutes at 7000 rpm at 4°C, the plasma was stored at minus 20°C. Concentrations of plasma atrial natriuretic peptide were measured by a kit from INC Holland by radioimmunoassay after extraction on Sep-Pak C-18 cartridges.[10] We have tested the kit in our laboratory: intra-assay and interassay variation did not exceed 5% and 10%, respectively, within the useful range ($B = 15$–85% of B_0 where B is the count for the standard (or sample) and B_0 is the count for the standard without atrial natriuretic peptide). Recovery of added atrial natriuretic peptide was 99%. Sensitivity was 0 8 pg/tube (4 pg/ml (1·3 pmol/l) plasma).

Statistical analysis was performed by Student's *t* test for paired and unpaired data. The dependence of the plasma concentration of atrial natriuretic peptide on the amount of work was examined by analysis of variance on the logarithm of the plasma concentration of atrial natriuretic peptide (figure). A p value < 0.05 was considered to be significant.

Results

Age, weight, and body surface area were similar in the trained and the untrained groups.

Table 1 shows echocardiographic results. The left ventricular mass was bigger in the athletes ($p < 0.0001$). Each athlete had a calculated left

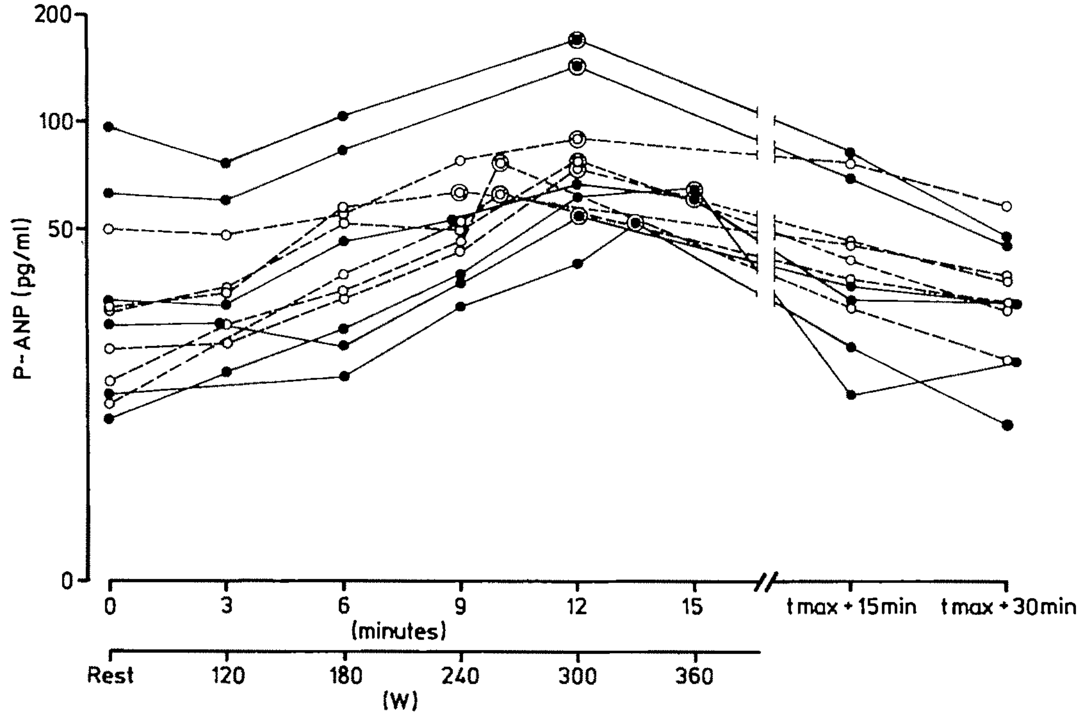


Figure *Response of plasma concentration of atrial natriuretic peptide (on a logarithmic scale) to graded exercise on a bicycle ergometer. Closed circles, athletes; open circles, untrained controls; double circles, maximum exercise. 1 pg/ml of atrial natriuretic peptide = 0·325 pmol/l.*

Table 1 *Measurements in athletes and controls (mean (SD))*

	Athletes (n = 6)	*Controls (n = 6)*	*p*
Age (yr)	25·8 (2·3)	24·2 (4·2)	0·4
Height (cm)	182 (7·4)	182 (3·8)	0·9
Weight (kg)	75·7 (8·7)	73·5 (7·3)	0·7
Body surface area (m²)	1·97 (0·15)	1·94 (0·11)	0·7
Pulse rate.			
At rest	60·3 (0·8)	95·0 (18·7)	0·001
At maximal work	187 (13·7)	192 (7·5)	0·5
BP(s)			
At rest (mm Hg)	121 (11)	118 (10)	0·7
At max work (mm Hg)	195 (14)	185 (15)	0·26
Maximal work (W)	325 (30)	277 (27)	0·01
Left atrium (mm)	35·2 (1·7)	30·7 (4·1)	0·03
LV ESD (mm)	34·8 (3·3)	33·8 (2·0)	0·5
LV EDD (mm)	55·8 (4·9)	47·7 (2·9)	0·005
Interventricular septum (mm)	10·3 (1·2)	8·33 (1·0)	0·01
LV posterior wall (mm)	11·0 (0·9)	8·67 (0·8)	0·001
LV fractional shortening (%)	37·7 (3·7)	29·0 (2·5)	0·001
LV ejection fraction (%)	76·8 (3·8)	67·1 (3·2)	0·001
LV mass (g)	299 (28)	170 (15)	<0·0001

BP(s), systolic blood pressure, LV, left ventricular, ESD, end systolic diameter, EDD, end diastolic diameter.

ventricular mass that was above normal (2·11–4·08 SD above normal mean), whereas all the controls had a left ventricular mass within the normal range (±2 SD of normal mean). The diameters of the left atria did not exceed the normal range. The calculated left ventricular fractional shortening and ejection fraction were below the upper normal limits.

The athletes had a larger left atrium, a larger left ventricular end diastolic dimension, thicker interventricular septum and left ventricular posterior wall, and a greater left ventricular fractional shortening than the control group. The left ventricular end systolic dimension was similar in both groups.

The pulse rate at rest was higher in the non-athletes than in the athletes, probably because the non-athletes were more nervous before the exercise test. The blood pressure both before and during the exercise test was similar in the two groups. As expected the athletes reached a higher maximum workload.

Table 2 *Plasma concentration of atrial natriuretic peptide at rest and at maximum work in athletes and non-athletes (mean (SD))*

P-ANP	*Athletes (n = 6)*	*Controls (n = 6)*	*p*
At rest (pg/ml)	41·4 (32·1)	28·0 (12·1)	0·6
At max work (pg/ml)	90·6 (52·1)	74·5 (10·1)	0·5
Increase (pg/ml)*	49·2 (22·4)	46·5 (9·13)	0·8
Factor†	2·57 (0·94)	2·95 (0·92)	0·5

P-ANP, plasma atrial natriuretic peptide.
*P-ANP at maximal work − P-ANP at rest.
†P-ANP at maximal work/P-ANP at rest.
1 pg/ml = 0·325 pmol/l.

The figure shows the values of the plasma atrial natriuretic peptide on a logarithmic scale for the athletes and the controls before, during, and after exercise. Both the untrained and trained men had a significant rise in the concentration of atrial natriuretic peptide during exercise. There were no differences between the two groups in plasma concentrations of atrial natriuretic peptide at rest, at any workload, at maximal workload, or after the exercise. The factor by which the plasma atrial natriuretic peptide concentration rose during the exercise test was similar in both groups (table 2). Therefore the data were pooled in order to obtain plasma concentrations of atrial natriuretic peptide for all the healthy young men both at rest and at maximum workload (table 3).

There was no correlation between the plasma concentration of atrial natriuretic peptide at rest and any of the variables measured during echocardiography ($r \leqslant 0·36$, $p \geqslant 0·25$). Despite the fact that atrial natriuretic peptide is produced in the atrial wall the correlation between plasma atrial natriuretic peptide and the diameter of the left atrium was only 0·21 ($p = 0·5$). Further, both the blood pressure and the pulse rate were correlated poorly with the plasma concentration of atrial natriuretic peptide.

Discussion

It is known that the heart is hypertrophic and dilated in well-trained athletes.[4,5] In our male athletes we found a significantly increased diastolic cavity dimension, left ventricular posterior wall, interventricular septal thickness, left ventricular ejection fraction, and left ventricular mass compared with our untrained controls. These observations have been described earlier.[11,12]

We were unable to show any difference in the plasma concentration of atrial natriuretic peptide between the trained and the untrained group, even though the heart was significantly larger in the athletes than in the control subjects.

Physiological hypertrophy of the heart, as seen in athletes after a period of intensive training, does not seem to influence the plasma concentration of atrial

Table 3 *Plasma concentrations of atrial natriuretic peptide (P-ANP) at rest and maximal work in 12 healthy young men*

P-ANP	*Mean*	*SEM*	*Range*
At rest (pg/ml)	34·7	6·97	14·5–96·5
At max work (pg/ml)	82·5	10·6	51·5–172
Increase (pg/ml)	47·8	4·73	27·5–78·5
Factor	2·76	0·26	1·78–4·28

See footnote to table 2.

natriuretic peptide or the release of atrial natriuretic peptide during exercise.

It is known that excretion of plasma atrial natriuretic peptide increases during exercise.[2 13] Plasma atrial natriuretic peptide is controlled by stretch receptors in the left and right atria of the heart. The plasma concentrations of atrial natriuretic peptide during chronic or acute cardiac failure correlated with pulmonary capillary wedge pressure.[14 15] Because pulmonary capillary wedge pressure increases during exercise,[16] the rising concentrations of plasma atrial natriuretic peptide during exercise may be a response to the stretch that results from the increased pressure in the left atrium. The plasma concentrations of atrial natriuretic petide did not differ in the athletic and non-athletic groups in our study. This suggests that there was no difference in the left atrial pressure between the two groups either at rest or during exercise. As far as we know this has not been reported before.

Although the left atrium was larger in the athletes than in the controls, the correlation between this enlargement and plasma concentrations of atrial natriuretic peptide at rest was only minor and not statistically significant. A similarly poor correlation between the left atrium measured by echocardiography and the plasma concentration of atrial natriuretic peptide ($r = 0{\cdot}28$, $p > 0{\cdot}2$) was described in 30 patients with various heart diseases or no heart disease at all, who were referred for routine echocardiography,[17] whereas a good correlation ($r = 0{\cdot}61$, $p < 0{\cdot}01$) between the size of the left atrium and the plasma concentration of atrial natriuretic peptide was reported in 14 patients with various organic heart diseases.[18] The plasma concentration of atrial natriuretic peptide may therefore reflect the size of the left atrium in the sick and failing heart, while the size of the left atrium is of little, if any, importance to the plasma concentration of atrial natriuretic peptide released by the healthy heart.

In patients with chronic heart failure, the heart works harder, and this will result in a hypertrophy of the heart. A production of atrial natriuretic peptide in this condition might be detected not only in the myocytes of the atria, but also in the ventricular myocytes.[19 20] The mechanisms responsible for the ventricular production are unknown. As in the atria, stretching of the muscle wall may trigger the production of the peptide by the ventricle.[21] It has been suggested that the higher concentrations of the peptide in the failing ventricles may be the result of hypertrophy. Our results indicate that hypertrophy does not initiate a production of natriuretic peptide in the ventricles sufficiently to increase significantly the concentration of plasma atrial natriuretic peptide above that in normal people with non-hypertrophic hearts.

We conclude that plasma atrial natriuretic peptide increases by a factor of about 2·8 during maximum exercise in healthy young men. Neither the size of the chambers of the left side of the heart nor left ventricular hypertrophy seem to be important to the concentration of plasma atrial natriuretic peptide during rest and exercise.

This study was supported by grants from the medical research council of the county of Funen. Statistical support was obtained from the Danish Medical Research Council.

References

1 Lang RE, Thoelken H, Ganten D, Luft FC, Ruskoaho H, Unger Th. Atrial natriuretic factor—a circulating hormone stimulated by volume loading. *Nature* 1985;314:264–6.

2 Bollerslev J, Svanegaard J, Blaabjerg O, Pindborg T. Atrial natriuretic peptide in relation to physical exercise. *Scand J Clin Lab Invest* 1987;47·681–5.

3 Henschen HE. *Eine medizinische Sportstudie. Skilauf und Skiwettlauf in Uppsala. Mitteilungen aus der medizinishen Klinik.* Jena: Fischer, 1899.

4 Nishimura T, Yoshihasa Y, Kawai C. Echocardiographic evaluation of long-term effects of exercise on left ventricular hypertrophy and function in professional bicyclists. *Circulation* 1980;61:832–40.

5 Hauser AM, Dressendorfer RH, Vos M, Hashimoto T, Gordon S, Timmis GC. Symmetric cardiac enlargement in highly trained endurance athletes: a two dimensional echocardiographic study. *Am Heart J* 1985;109:1038–44.

6 Sahn DJ, DeMaria A, Kisslo J, Weyman A. Recommendations regarding quantitation in M-mode echocardiography: results of a survey of echocardiographic measurements. *Circulation* 1978;58: 1072–83.

7 Troy BL, Pombo J, Rackley CE. Measurements of left ventricular wall thickness and mass by echocardiography. *Circulation* 1972;45:602–11.

8 Henry WL, Gardin JM, Ware JH. Echocardiographic measurements in normal subjects from infancy to old age. *Circulation* 1980;62:1054–61.

9 Savage DD, Abbott RD, Anderson SJ, Padgett S. Determinants of left ventricular mass and reference values based on a large population-based sample of apparently healthy subjects: the Framingham study [Abstract]. *Circulation* 1983;68(suppl 3):336.

10 Rosmalen FMA, Tan ACITL, Tan HS, Benraad TJ. A sensitive radioimmunoassay of atrial natriuretic peptide in human plasma, using a tracer with an immobilized glucouril agent. *Clin Chim Acta* 1987; 165:331–40.

11 Fagard R, Aubert A, Staessen J, Eynde EV, Vanhess L, Amery A. Cardiac structure and function in cyclists and runners. Comparative echocardiographic study.

Br Heart J 1984;52:124–9.

12 Shapiro LM. Physiological left ventricular hypertrophy. *Br Heart J* 1984;52:130–5.

13 Follenius M, Brandenburger G. Increase in atrial natriuretic peptide in response to physical exercise. *Eur J Appl Physiol* 1988;57:159–62.

14 Richards AM, Cleland JGF, Tonolo G, *et al.* Plasma alpha natriuretic peptide in cardiac impairment. *Br Med J* 1986;293:409–12.

15 Matsubara H, Nishikawa M, Umeda Y, *et al.* The role of atrial pressure in secreting atrial natriuretic polypeptides. *Am Heart J* 1987; 113:1457–63.

16 Yoshida A, Kadota K, Kambara H, *et al.* Left ventricular responses to supine exercise assessed by radionuclide angiocardiography and a Swan-Ganz catheter. *Jpn Circ J* 1985;49:661–71.

17 Crozier JG, Nicholls MG, Ikram H, Espiner EA. Relation between left atrial diameter and plasma atrial natriuretic peptide. *Am J Cardiol* 1986;58:1134–6.

18 Haass M, Fischer TA, Dietz R. Is atrial distension the physiological stimulus for release of atrial natriuretic peptide? *Lancet* 1987;ii:1269–70.

19 Nemer M, Lavigne J-P, Drouin J. Ventricular atrial natriuretic factor gene expression: a marker for cardiac hypertrophy [Abstract]. *J Cell Biochem* 1988;suppl 12A:17.

20 Edwards BS, Ackermann DM, Lee ME, Reeder GS, Wold LE, Burnett JC Jr. Identification of atrial natriuretic factor within tissue in hamsters and humans with congestive heart failure. *J Clin Invest* 1988;81:82–6.

21 Galipeau J, Nemer M, Drouin J. Ventricular activation of atrial natriuretic factor gene in acute myocardial infarction. *N Eng J Med* 1988;319:654–5.

Br Heart J 1989;62:450–4

Clinical course of endomyocardial fibrosis

PRABHA N GUPTA, MARTHANDAVARMA S VALIATHAN, KUMARALINGAM G BALAKRISHNAN, CHANDRASEKHARAN C KARTHA, MRINAL K GHOSH*

*From the Indian Council of Medical Research Centre for Research in Cardiomyopathies, Sree Chitra Tirunal Institute for Medical Sciences and Technology and *Quality Assurance Division, Vikram Sarabhai Space Centre, Trivandrum, India*

SUMMARY The survival pattern, morbidity, and clinical course of 145 patients with endomyocardial fibrosis who were followed up between November 1975 and June 1987 were studied. The diagnosis was confirmed in all cases by cardiac angiography, or echocardiography, or necropsy. Percentage survival at the end of one and 9·5 years was 76·11 and 26·35 respectively.

History, physical examination, electrocardiography, and cardiac catheterisation were studied at the first presentation. The determinants of early mortality were studied by univariate Kaplan-Meier estimates compared by the log rank test and Cox proportional hazards multiple regression analysis. Significant univariate predictors of early mortality were QRS axis above +90°, intraventricular conduction delay (QRS duration $>0·12$ s), duration of symptoms before presentation, New York Heart Association functional classes III and IV, presence of embolic episodes, right atrial mean pressures >20 mm Hg, right ventricular end diastolic pressure >20 mm Hg, and aortic oxygen saturation $<85\%$. The significant multivariate predictors of mortality were cyanosis, New York Heart Association functional class at first presentation, and right atrial mean pressure >20 mm Hg.

The bleak prognosis of endomyocardial fibrosis did not substantially improve despite advances in the medical management of congestive cardiac failure during the period of the study.

Endomyocardial fibrosis has been extensively characterised in terms of clinical,[1] radiological,[2] and echocardiographic features,[3] and its surgical management standardised in recent years.[4 5] There have, however, been few studies on its clinical course.[6] We report on the clinical course of endomyocardial fibrosis in the south western state of Kerala in India, where the disease is prevalent.

Patients and methods

One hundred and forty five patients in whom the diagnosis was confirmed by cardiac angiography (121), echocardiography (2), or necropsy (17) or both angiography and necropsy (5) and who were followed from November 1975 to June 1987 form the basis of this report. Forty six patients who were treated by endocardiectomy and valve replacement during the same period were excluded because they were the subject of a detailed report.[4]

CLINICAL FEATURES

Table 1 lists the clinical features of patients in the present series. The mean (SD) age of the patients at first presentation was 26·3 (14·1) years for women (n = 70) and 21·1 (11·9) years for men (n = 75); 33·1% were under 15. Thirty one (21%) patients had had symptoms for less than 2 years before presentation to the hospital. Seventy two (49.7%) were in New York Heart Association functional classes III and IV at first presentation. The proportion of patients with right and left heart failure was the same at first presentation (37·9%). Apart from atrial fibrillation, arrhythmias were uncommon in these patients. Ventricular extrasystoles were seen in five (3·4%). Sixteen (11·03%) of the patients were anaemic (haemoglobin <100 g/l). The large proportion of patients belonging to the New York Heart Association classes III and IV (49·7), with ascites (40·0%), peripheral oedema (24·8%), cardiothoracic ratio $>60\%$ (57·2%), and other features show how

Requests for reprints to Dr Marthandavarma S Valiathan, Sree Chitra Tirunal Institute for Medical Sciences and Technology, Trivandrum 695011, Kerala, India.

Accepted for publication 10 August 1989

Table 1 *Clinical profile of 145 patients with endomyocardial fibrosis at first presentation*

Variable	*Percentage*
Febrile illness at onset	9·7
Atypical or anginal chest pain	13·1
Duration of symptoms <24 months	21·4
Swelling of the lower limbs	24·8
New York Heart Association classes III and IV	49·7
Below the age of 15 years	33·1
Right heart failure at first presentation	37·9
Left heart failure at first presentation	37·9
Cyanosis	15·9
Ascites	40·0
Clubbing of digits	11·0
No murmurs at first presentation	26·2
Cardiothoracic ratio >0·6	57·2
Haemoglobin <100 g/l	11·0
Absolute eosinophil count >2000/μl	11·7
Atrial fibrillation	32·4
Ventricular extrasystoles	3·4
Junctional rhythm, or heart block	3·4
Right axis deviation (> +90°)	31·7
Intraventricular conduction delay (QRS >0·12 s)	21·4

severe and advanced the disease was when the patients sought medical attention. The distribution of eosinophil counts in the patients varied as follows: 0–500/μl, 54 (37·2%); 501–1000/μl, 30 (20·7%); 1001–1500/μl; 25 (17·2); 1501–2000/μl, 19 (13·1). Eosinophilia of >2000/μl was seen in 17 patients (11·7%).

ECHOCARDIOGRAPHY

Echocardiographic data were available in 86 patients. The mean (SD) left ventricular internal dimensions in diastole and systole were 4·17 (1·19) cm and 2·9 (1·07) cm respectively. Pericardial effusion was present in 35 (40·7%), intracavitary thrombi in 11 (12·8%), and myocardial calcification in 16 (18·6%) patients.

CARDIAC CATHETERISATION

Right and left heart catheterisation was performed in 126 patients and the cardiac output and index calculated by the Fick method. Diagnosis of endomyocardial fibrosis was established in these patients on the basis of angiographic features.[7] Table 2 summarises the data from cardiac catheterisation and angiography.

FOLLOW UP

All patients were regularly followed every 6 months by prior appointment. Patients were also referred by the local physician or came on their own because of symptoms. Patients who did not attend were sent at least three postal reminders. Information on deaths at home was available from the relatives of 21 patients. Nineteen patients were lost to follow up during the first year. Repeat angiograms were performed in twelve patients during the follow up period.

STATISTICAL ANALYSIS

All patient variables for those surviving one year and those who died were compared by a t test for quantitative data and a χ^2 test for qualitative data. The significant variables in this analysis were chosen for the log rank test. Nineteen clinical variables and seven haemodynamic ones (from cardiac catheterisation) were analysed for their impact on survival by the log rank test.[8]

Cox proportional hazards multiple regression analysis[9] was also applied to the variables studied by the log rank test. We used a BIOSTAT program.

Cox proportional hazards regression analysis of the seven haemodynamic variables was also carried out in patients with predominant involvement of the right ventricle and of the left ventricle.

Programs were written in CDC Cyber Fortran IV language. The linearity assumption was validated by the analysis of variance technique, and the significance of the predictor variables was studied by the F test.

Results

During the follow up of 334 patient years, 25 embolic episodes of the territories of the iliofemoral (6), pulmonary (10), carotid (8), and mesenteric arteries (1) developed in 24 patients. Three of the patients presenting without murmurs developed regurgitant

Table 2 *Data (mean (SD)) from cardiac catheterisation in 126 patients with endomyocardial fibrosis*

Predominant involvement	*Total number*	*Involvement of contralateral ventricle*	*Mean RA pressure*	*Mean RVEDP*	*Mean LVEDP*	*PA mean pressure*
RV	66	56	18·04 (6·70)	18·30 (6·20)	15·19 (6·30)	24·15 (14·20)
LV	45	33	11·40 (7·50)	15·44 (9·40)	23·27 (8·30)	38·34 (18·01)
BV	15	15	14·10 (8·44)	19·16 (10·16)	24·53 (6·50)	33·46 (12·60)

RV, right ventricular endomyocardial fibrosis; LV, left ventricular endomyocardial fibrosis; BV, biventricular endomyocardial fibrosis, RA, right atrial, LVEDP, left ventricular end diastolic pressure; RVEDP, right ventricular end diastolic pressure; PA mean, pulmonary artery mean pressure.

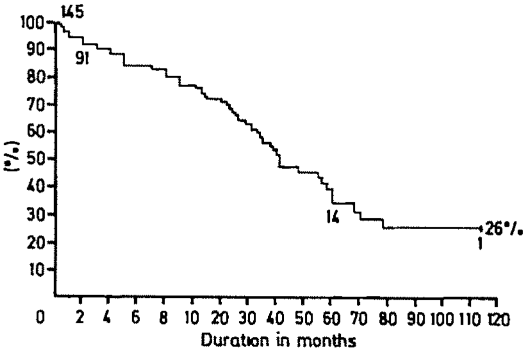
Table 3 *Cause of death in 66 patients with endomyocardial fibrosis who died during follow up of 11 years 7 months*

	No	*Percentage*
Congestive cardiac failure	16	24 2
Severe right ventricular failure, hepatic coma	9	13 6
Embolic phenomena	11	16 7
Terminal arrhythmias	6	9·0
Unknown causes (death at home informed by letter)	21	31 8
Others*	3	4 5

*Meningitis (1), Drug allergy (1), chronic obstructive airway disease (1).

murmurs after a year of follow up. Eleven developed ascites, four atrial fibrillation, and four evidence of ventricular hypertrophy on the elctrocardiogram at varying intervals after the first presentation.

Of our series of 145 patients, 66 died during the follow up period of 334 patient years. Table 3 shows the causes of death. Of the 66 deaths, 32 occurred during the first year of follow up (25·4%). The survival rate was 76·1% at the end of one year, 68·0% at 2 years, 35·6% at 5 years, and 26·4% after 9·5 years (figure).



Survival curve (Kaplan-Meier) of 145 patients with endomyocardial fibrosis. Numbers are individuals at risk.

NECROPSY

Necropsies were performed in 22 patients who died in the hospital.[10] Eighteen had obliteration of both ventricular cavities. The trabecular portion and papillary muscles were seen to be particularly vulnerable to fibrotic changes. The causes of death in this group were congestive cardiac failure, bronchopneumonia, or embolic episodes. Cavity obliteration of the right ventricle alone was seen in three patients. In one, the left ventricle alone was affected. In two who were diagnosed to have pure left ventricular endomyocardial fibrosis at angiography, necropsy showed obliteration of the apex and some involvement of the trabecular portion of the right ventricle.

UNIVARIATE ANALYSIS

The factors significantly affecting survival were considerable anaemia (haemoglobin < 100 g/l), development of embolic episodes, QRS axis more than +90°, delayed intraventricular conduction (QRS duration > 0·12 s), New York Heart Association classes III and IV, a short symptomatic history before admission to hospital, the presence of cyanosis, and left and/or right ventricular failure at first

Table 4 *Selected clinical variables that were significant in univariate analysis in 145 patients with endomyocardial fibrosis*

Prognostic factor	*No*	*Percentage survival*			*p value**
		At 1 year	*At 2 years*	*At 5 years*	
Duration of symptoms before presentation:					
< 24 months	31	38 14	None	None	
> 24 months	114	83 68	77 32	40 46	<0 01
Cyanosis:					
Absent	122	80 83	71 46	36 93	
Present	23	46 99	39·16	31·32	<0 01
Haemoglobin:					
< 100 g/l	16	36 45	27 34	13 67	
> 100 g/l	129	80 45	73 27	40 14	<0 01
QRS axis:					
< +90°	99	82·56	77 36	47·78	
> +90°	46	61 77	48 03	8·89	<0 01
Intraventricular conduction delay QRS duration(s).					
<0·12	114	80·14	72·34	42 92	
>0·12	31	60 5	51 5	19 20	<0 01
New York Heart Association class.					
I and II	73	82 7	75 59	47 09	
III and IV	72	65·34	59 55	23 42	<0 01
Embolic phenomenon:					
Absent	120	80 99	74 7	38 56	
Present	25	45·72	28 58	19 05	<0 01

*Log rank test of Kaplan-Meier estimates.

Table 5 *Univariate analysis of 126 catheterised patients with endomyocardial fibrosis (mortality determinants by log rank test of Kaplan-Meier estimates)*

Variable	*No*	*% survival at 1 year*	*% survival at 2 years*	*% survival at 5 years*	*p*
RA mean pressure:					
<20 mm Hg	93	83·7	68·7	42·5	
>20 mm Hg	33	57·2	36·4	19·4	<0·01
RVEDP.					
<20 mm Hg	90	87·7	72·1	39·7	
>20 mm Hg	36	48·0	31·5	15·7	<0·01
LVEDP:					
<15 mm Hg	56	79·2	61·6	39·8	
>15 mm Hg	70	74·1	59·5	27·4	NS
Aortic oximetry:					
<85%	14	60·6	43·3	10·8	
>85%	112	78·1	62·6	43·5	<0·01

RA, Right atrial; RVEDP, right ventricular end diastolic pressure; LVEDP, left ventricular end diastolic pressure.

presentation (table 4). The analysis showed that age, sex, and predominantly right or left ventricular endomyocardial involvement had no effect on survival.

The haemodynamic data showed that right atrial mean pressures >20 mm Hg, right ventricular end diastolic pressure >20 mm Hg, and aortic oxygen saturation of <85% were associated with significantly shorter survival (table 5). The value of left ventricular end diastolic pressure, pulmonary artery mean pressure, aortic mean pressure, and pulmonary artery oxygen saturation had no significant effect on survival.

MULTIVARIATE ANALYSIS

The most important multivariate predictors of survival were cyanosis, New York Heart Association class at first presentation, and right atrial mean pressures above 20 mm Hg (table 6). Because separate analysis of the predominant involvement of the right and left ventricular endomyocardial fibrosis did not yield any significant information, the results of analysis of pooled data are presented.

PROGRESSION OF ENDOMYOCARDIAL FIBROSIS

Twelve patients had repeat cardiac catheterisation over a period of 2–3 years. Of these, eight had angiographic progression of the disease. Three showed advancement of the disease in the same ventricle and five had new involvement of the previously uninvolved ventricle during the repeat study. Three patients with left ventricular disease developed partial right ventricular obliteration within 12, 24, and 28 months respectively. Two of them also developed tricuspid regurgitation. Left ventricular apical obliteration developed within 12 months in two patients with right ventricular disease; mitral regurgitation also developed in one.

Table 6 *Cox proportional hazards multivariate analysis of clinical and haemodynamic determinants of mortality*

Variable	*p value*
Cyanosis—present or absent	0·003
Right atrial mean pressure> <20 mm Hg	0·002
NYHA class I and II *v* III and IV	0·008

NYHA, New York Heart Association.

Discussion

Previous reports on the clinical course of endomyocardial fibrosis were generally based on the study of smaller numbers of patients.[6] The main objective of the present study was to follow the natural history of patients with endomyocardial fibrosis after their first presentation to the hospital. Our present data suggest that the disease has a less unfavourable course than what was previously reported by D'Arbela *et al* who noted that 43·5% of their patients died in the first year of follow up with the death of a majority of patients taking place in 3–4 years.[11] Parry and Abrahams followed patients with endomyocardial fibrosis and found their clinical course to be varied and marked by rapid deterioration, chronicity, or acute on chronic manifestations.[6] We have noted similar patterns of survival in the present study. The early deaths among patients presenting with a clinical history of less than two years which proved to be a significant univariate predictor of mortality suggested a more severe and rapidly fatal form of endomyocardial fibrosis distinct from the chronic form of the disease. It is also possible that the first two years after the onset of symptoms represented the acute phase of the disease and patients who survived this stormy period might progress to a chronic "burnt-out" phase with longer survival. The grave prognosis of the acute phase is corroborated by the series of D'Arbela and colleagues who reported that 43·5% of their patients died during the first year.

We found cyanosis to be a significant multivariate determinant of survival. The restriction of ventricular compliance and the high right ventricular end diastolic pressure, which stretches open the foramen ovale and causes a right to left shunt, explains the prognostic significance of cyanosis.

Among the significant electrocardiographic criteria for survival, a QRS axis of more than + 90° is likely to be caused by dilatation of the right ventricular outflow tract with delayed activation of that region or right ventricular preponderance secondary to severe pulmonary hypertension. Right ventricular failure at first presentation as shown by raised right ventricular end diastolic pressure was also shown to influence survival adversely.

In common with other reports on endomyocardial fibrosis from Kerala[12] we found no significant eosinophilia in the present series. Statistical analysis did not show eosinophilia to be a significant determinant of survival.

Surprisingly left ventricular end diastolic pressure and pulmonary artery mean pressure were not found to be significant determinants of early mortality when analysed separately even in predominantly left ventricular endomyocardial fibrosis. We speculate that this paradoxical finding may be due to the early stage of the disease, when patients with left ventricular endomyocardial fibrosis tend to seek medical attention with distressing symptoms like dyspnoea. In contrast, patients with right ventricular endomyocardial fibrosis approach hospitals at a late stage with advanced features of the disease such as obliteration of the right ventricular inflow and frank right ventricular failure. It seems that raised left ventricular end diastolic pressure and pulmonary artery mean pressure are subsumed by the early phase of the disease when the functional reserve of the left ventricle is substantially unimpaired.

Echocardiography has several limitations in quantifying the morphological changes in endomyocardial fibrosis and seems to be a weak tool in the prediction of survival. For example, an irregularly shaped chamber may give inaccurate measurements of left ventricular dimensions at the chordal level because the apical portion of the ventricle alone may be involved by fibrosis in the initial stage of the disease.

Several factors were shown to influence significantly the course of patients with endomyocardial fibrosis in the present series but predominant involvement of a particular ventricle was not one of them. This is probably because endomyocardial fibrosis is essentially a biventricular disease—both angiography and necropsy show fewer cases with one affected ventricle. Furthermore, the angiographic progression of the disease towards the involvement of the previously unaffected ventricle in five cases also points to the biventricular nature of the disease.

Even though the grave prognosis of endomyocardial fibrosis has long been known, we attempted to identify the determinants of survival on the basis of clinical, haemodynamic, necropsy, and follow up data in 145 patients in the south western state of Kerala in India. In an earlier report from this institution, two year survival among 46 patients who underwent endocardiectomy and valve replacement was 67% and 29 patients showed a significant improvement in their functional class.[4] The survival rate at 5 years and 8 months was 60·8%. It seems that the outcome in surgically treated patients is better than their medically treated counterparts who are reported in the present study.

PNG thanks the Indian Council of Medical Research for financial support. We thank the Institute for the use of facilities in the study and the Vikram Sarabhai Space Centre for the use of the computer.

References

1 Valiathan MS, Balakrishnan KG, Kartha CC. A profile of endomyocardial fibrosis. *Indian J Pediatr* 1987;54:229–36.

2 Sasidharan K, Kartha CC, Balakrishnan KG, Valiathan MS. Early angiographic features of right ventricular endomyocardial fibrosis. *Cardiology* 1983;70:127–31.

3 Vijayaraghavan G, Davies J, Sadanandan S, Spry CJF, Gibson DG, Goodwin JF. Echocardiographic features of tropical endomyocardial disease in South India. *Br Heart J* 1983;50:450–9.

4 Valiathan MS, Balakrishnan KG, Sankarkumar R, Kartha CC. Surgical treatment of endomyocardial fibrosis. *Ann Thorac Surg* 1987;43:68–73.

5 Balakrishnan KG, Venkitachalam CG, Pillai VRK, Subramanyan R, Valiathan MS. Post-operative evaluation of endomyocardial fibrosis. *Cardiology* 1986;73:73–84.

6 Parry EH, Abrahams DG. The natural history of endomyocardial fibrosis. *Q J Med* 1965;34:383–408.

7 Sasidharan K, Balakrishnan KG, Venkitachalam CG, Sapru RP. Radiological features of endomyocardial fibrosis: In: Sapru RP, ed. *Endomyocardial fibrosis in India.* New Delhi: ICMR, 1983:90–103.

8 Mathews DE, Farewell V. *Using and understanding medical statistics.* New York· Karger, 1985:67–87.

9 Kalbfleisch JD, Prentice RI. *The statistical analysis of failure time data.* New York: Wiley, 1980:70–117.

10 Kartha CC, Sandhyamani S. An autopsy study of tropical endomyocardial fibrosis in Kerala. *Indian J Med Res* 1985;82:439–46

11 D'Arbela PG, Mutazindwa T, Patel AK, Somers K. Survival after first presentation with endomyocardial fibrosis. *Br Heart J* 1972:34:403–7.

12 Sapru RP, Balakrishnan KG, Iyer KS, Shanmugham J, Asok PP, Sehgal S. Haematological, biochemical, immunological and electrophysiological studies in endomyocardial fibrosis. In: Sapru RP, ed. *Endomyocardial fibrosis in India.* New Delhi: ICMR, 1983:175–82.

Br Heart J 1989;62:455–61

Right ventricular function 10 years after the Mustard operation for transposition of the great arteries: analysis of size, shape, and wall motion

ANDREW N REDINGTON, MICHAEL L RIGBY, PAUL OLDERSHAW,
DEREK G GIBSON, ELLIOT A SHINEBOURNE

From the Brompton Hospital, London

SUMMARY Biplane right ventriculograms were obtained in 18 symptom free patients 109 (26) months (mean (SD)) after Mustard repair of transposition of the great arteries. Ventricular size, shape, and wall motion were measured from the digitised angiograms and compared with previously published data on left ventricular function after anatomical correction of transposition of the great arteries, with right ventricular function in controls, and with patients before repair of tetralogy of Fallot. Global indices of ventricular function were depressed after Mustard repair and wall motion abnormalities were common. The presence of wall motion abnormalities in this group was associated with a reduction in ejection fraction and ventricular filling rates. In four of five patients in whom an appropriate preoperative angiogram was available a similar pattern of wall motion was seen before the Mustard operation, suggesting that preoperative events may be important in determining eventual outcome.

The choice between intra-atrial repair[1] or anatomical correction[2] for patients with transposition of the great arteries remains a subject of debate. Few would question the considerable impact that intra-atrial procedures have had on early and mid-term survival in these patients,[3 4] but the ability of the right ventricle to function adequately as the systemic pumping chamber in the long term was questioned after earlier reports of right ventricular dysfunction after these operations.[5 6] Anatomical correction has the theoretical advantage of restoring the left ventricle as the systemic ventricle. Indeed several postoperative studies showed global left ventricular function that almost equalled that of the normal left ventricle.[7–10] The higher early mortality of the operation was perhaps its biggest drawback, but with improved surgical techniques the operation is being performed earlier in life, and surgical mortality has improved. Comparisons of functional results after these operations are therefore of increasing importance.

In this study, data on right ventricular function were obtained from a large group of patients studied 7–10 years after a Mustard operation for simple transposition of the great arteries. We compared these data with our earlier data on right ventricular function in controls,[11] in patients with right ventricular pressure load,[12] and with left ventricular function studied early after anatomical correction.[10]

Patients and methods

PATIENTS AFTER THE MUSTARD PROCEDURE

This group consisted of 18 patients (mean (SD) age 118 (24) months) studied 109 (26) months after a Mustard operation for repair of transposition of the great arteries. They were the group with the longest follow up at the Brompton Hospital. All patients had either an intact ventricular septum or a small ventricular septal defect that was haemodynamically unimportant and did not require surgical closure. Seventeen of the patients had required balloon atrial septostomy during the neonatal period. The mean (SD) age at Mustard operation was nine (6) months.

All were symptom free at the time of routine review in the outpatient department. Informed consent was obtained from the parents of each patient. Some of the patients in this group underwent, in addition, detailed haemodynamic studies, and this data is presented elsewhere.[13]

Requests for reprints to Dr Andrew N Redington, Department of Paediatric Cardiology, Brompton Hospital, Fulham Road, London SW3 6HP.

Accepted for publication 16 June 1989

PATIENTS AFTER ANATOMICAL CORRECTION

This group consisted of 15 patients, nine with simple transposition of the great arteries and six with transposition and a large ventricular septal defect.[10] They were studied 20 (15) months after anatomical correction. Their age at operation ranged from one day to 73 months. Those with simple transposition were operated on significantly earlier ($p < 0.02$, Mann-Whitney U test). Six patients had a significant obstruction of the right ventricular outflow tract (mean gradient 54 mm Hg), but no patient had obstruction of the left ventricular outflow tract or aortic regurgitation. Data from some of the patients in this group were included in an earlier report.[13]

OTHER GROUPS

We have earlier reported data on right ventricular function in 10 normal adults,[11] and in 12 patients studied before repair of tetralogy of Fallot.[12] These data gave us the opportunity to compare right ventricular function after the Mustard operation with right ventricular function under normal loading conditions and when the right ventricular pressure is at a systemic level. These groups are historical controls and conclusions drawn from such a comparison must be interpreted with caution.

ANALYSIS OF ANGIOGRAMS

Biplane right ventriculograms were obtained in 30° right oblique and 60° left oblique projections, and single plane left ventriculograms were obtained in 30° right oblique projections. Our method of analysis has been reported in detail elsewhere.[11] Each ventriculogram was digitised frame by frame and the following indices of function were derived from the stored data.

(a) Ventricular volumes

End diastolic, end systolic, and stroke volumes were measured from the volume-time curves and were normalised for body surface area (ml/m^2). The ejection fraction was calculated in the usual way. Ventricular filling and emptying rates were normalised by dividing by end diastolic volume.

(b) Volume independent indices

Because it was difficult to compare volume dependent indices of right and left ventricular function in these patients, we analysed two further aspects of function in detail. The analysis of ventricular shape and regional wall motion has the potential advantage of being independent of absolute size and so may be of particular value in such a comparison.

Ventricular shape index.—This is a measure of the "roundness" of the cavity outline throughout the cardiac cycle. Derived as 4π cavity area/perimeter it has a maximum value when the cavity outline is circular and a minimum value of 0 when there is complete obliteration of the cavity. During systole the normal left ventricle becomes less round, up to 20% of its stroke volume being ejected as a result of shape change alone.[14] The index has the advantage of being independent of ventricular size and has been used to examine changes in the mechanism of left ventricular ejection in babies and children.[7 10] The right ventricular end diastolic shape index was measured separately in the right anterior oblique and left anterior oblique views, and the change in the shape index during systole was taken as the difference between measurements at end diastole and at end ejection.

Regional wall motion.—Isometric and contour plots of regional wall motion throughout the cardiac cycle were made for each patient. This method depends on defining 40 equally spaced points around the outline of the end diastolic cavity.[15-17] From each of these points the nearest point on the end systolic outline is determined and the two points are joined. The position of the endocardium throughout the cardiac cycle was measured on each of these lines and expressed in millimetres from its end diastolic position. Thus 40 plots of endocardial motion throughout the cardiac cycle were generated. A three dimensional isometric display was produced by stacking the 40 plots obliquely with each plot connected by isochrones representing successive cine frames, or alternatively a contour map was produced with each contour representing movement of the endocardium by 1 mm from the end diastolic position (fig 1). The times of end systole (taken as minimum cavity volume) and mital or tricuspid valve opening (corresponding to the cineframe in which unopacified blood first entered the ventricle) were marked on both displays.

Left ventricular wall motion abnormalities were assessed by comparison with previously reported normal values.[15] No normal data are available for the right ventricle for this method of display. Instead wall motion was said to be abnormal if wall motion plots taken from the right oblique projection showed systolic outward motion of more than 2 mm in three or more adjacent segments (dyskinesia); inward motion in more than 3 adjacent segments continued beyond the time of tricuspid valve opening (isovolumic abnormalities); or if there was less than 2 mm of inward motion of more than 3 adjacent segments (hypokinesia).

STATISTICAL ANALYSIS

Variables were expressed as the mean (1 SD). Comparison of group data was by Student's t tests when the data were normally distributed and by non-

Table *Individual data from the 18 patients after Mustard's operation*

atient o.	*EDVI (ml/m²)*	*ESVI (ml/m²)*	*SVI (ml/m²)*	*EF (%)*	*PFR (s⁻¹)*	*tPFR (ms)*	*PER (s⁻¹)*	*tPER (ms)*	*RR (ms)*	*ED shape RAO*	*ED shape LAO*
1	82	19	63	76	3·7	110	2·16	240	950	87	81
2	107	43	64	59	2·7	30	3·8	100	540	82	74
3	77	31	46	59	4·3	40	5·3	100	460	82	84
4	89	34	54	61	3·5	120	3·9	70	480	80	91
5	78	49	29	37	1·38	90	1·2	100	820	91	82
6	64	28	36	56	2·9	110	2·8	80	620	89	80
7	104	77	27	26	2·38	40	1·1	90	300	90	75
8	53	27	26	49	3·9	80	3·3	110	450	92	70
9	76	37	39	51	2·9	50	3·7	150	500	90	78
0	60	16	44	73	5·5	80	7·5	110	440	75	74
1	66	33	33	50	4·1	60	3·9	90	400	85	71
2	70	51	19	27	1·1	60	2·0	110	540	89	75
3	107	64	43	40	1·1	100	2·3	120	800	78	95
4	107	48	59	55	4·2	110	4·9	190	1100	94	89
5	126	85	41	32	1·79	100	1·8	150	800	80	81
6	120	63	57	47	3·3	100	2·6	200	980	92	—
7	72	44	28	38	2·7	160	2·2	110	760	78	76
8	63	27	36	57	4·5	110	3·4	110	500	94	82

DVI, end diastolic volume index; ESVI, end systolic volume index; SVI, stroke volume index; EF, ejection fraction; PFR, peak filling rate; PER, peak jection rate; t, time, RAO, right anterior oblique, LAO, left anterior oblique.

parametric tests (Mann-Whitney U test) when they were not. Correlation of variables was examined by linear regression by the method of least squares.

Results

The table shows data from individual patients after operation. The results below are given as means (1 SD).

GLOBAL RIGHT VENTRICULAR FUNCTION

No patient had significant tricuspid regurgitation. The end diastolic volume index was 84·4 (22) ml/m². The end systolic volume index was 43 (19) and the stroke volume index was 41 (13·5) ml/m². The ejection fraction ranged from 26 to 76% (mean 50 (14)%; seven patients had an ejection fraction of <50%. The peak filling rate, corrected for end diastolic volume, was 3·1 (1·2) s^{-1} and correlated ($r = 0·76, p < 0·001$) with the ejection fraction. A similar relation between peak ejection rate and ejection fraction was also found ($r = 0·68, p < 0·001$).

The end diastolic shape index was 86 (6) in the right anterior oblique projection and 79 (7) in the left anterior oblique projection. The systolic shape change was 7·6 (5)% and 3·6 (4·3)% for right and left oblique projections respectively.

REGIONAL RIGHT VENTRICULAR FUNCTION

Examination of regional wall motion plots showed a "normal" pattern in nine patients (fig 1). The remainder showed one or more of the abnormalities described in the methods section. Of these nine patients, four had areas of hypokinesis, five showed areas of systolic dyskinesis (affecting the inflow portion of the right ventricle in four (fig 2), and there were isovolumic abnormalities in three, all of whom showed areas of inward wall motion after the time of tricuspid valve opening (fig 3).

Comparison of the subgroup of nine patients with wall motion abnormalities with nine with a "normal" pattern showed differences in global function. The right ventricular ejection fraction was lower in those with abnormalities (40 (11·5) *v* 59 (9·5)%, $p = 0·0015$) as was the peak filling rate (3·8 (0·9) *v* 2·4 (1·2) s^{-1}, $p = 0·018$). There was a tendency for the end systolic volume index to be higher in those with abnormal wall motion (35 (15) *v* 52 (20) ml/m², $p = 0·06$).

In view of these findings we studied the preoperative angiograms; 16 angiograms were available for review, but unfortunately only five of these were of adequate quality and in an appropriate angiographic projection for subsequent analysis. One was from a patient with "normal" postoperative wall motion. The preoperative wall motion plots were also normal in this patient. The remaining four angiograms came from patients shown to have postoperative wall motion abnormalities. Of these, one patient had "normal" preoperative right ventricular wall motion; the rest were abnormal. The similarity between preoperative and postoperative wall motion plots was striking, despite the long interval between studies. Figure 3 shows the isometric plots taken from preoperative and postoperative angiograms. Despite an interval of nine years, the two plots are similar. Both show areas of outflow tract hypokinesia, with peak inward movement of the inflow tract occurring after tricuspid valve opening. There was no relation between any of the indices and either age at operation or time from operation.

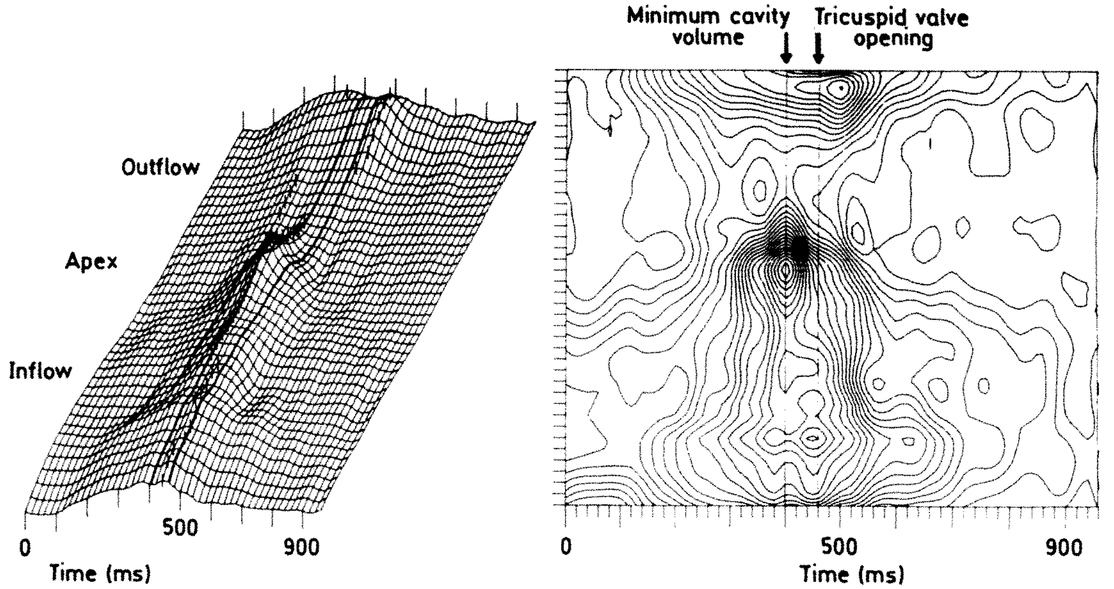


Fig 1 *Right ventricular wall motion plot from a patient after Mustard's operation. Wall motion is normal.*

COMPARISON WITH OTHER GROUPS

Left ventricle after anatomical correction[10]

The right ventricle was larger after a Mustard operation than the left ventricle was after anatomical correction at end diastole (anatomical correction 64 (21) ml/m^2), and end systole (anatomical correction 18 (9) ml/m^2). The ejection fraction was lower in the subgroup of patients with transposition and ventricular septal defect than in those with simple transposition (62 (9)% *v* 76 (10)%) but the right ventricular ejection fraction after a Mustard operation was lower than in the anatomical correction

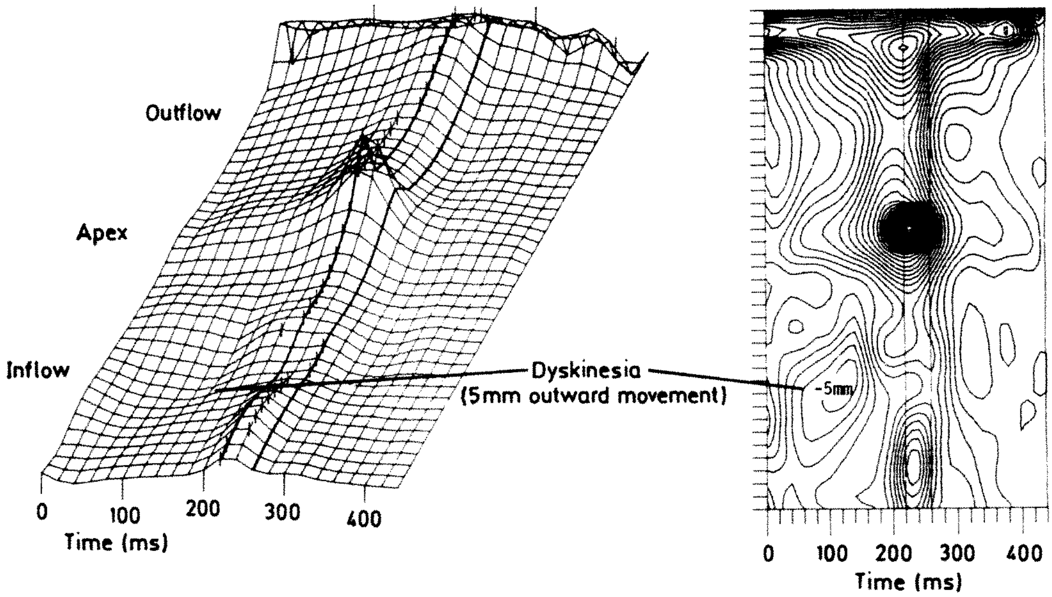


Fig 2 *Right ventricular wall motion plot from a postoperative patient. There is an area of systolic dyskinesis (5 mm outward movement) of the inflow portion of the ventricle.*

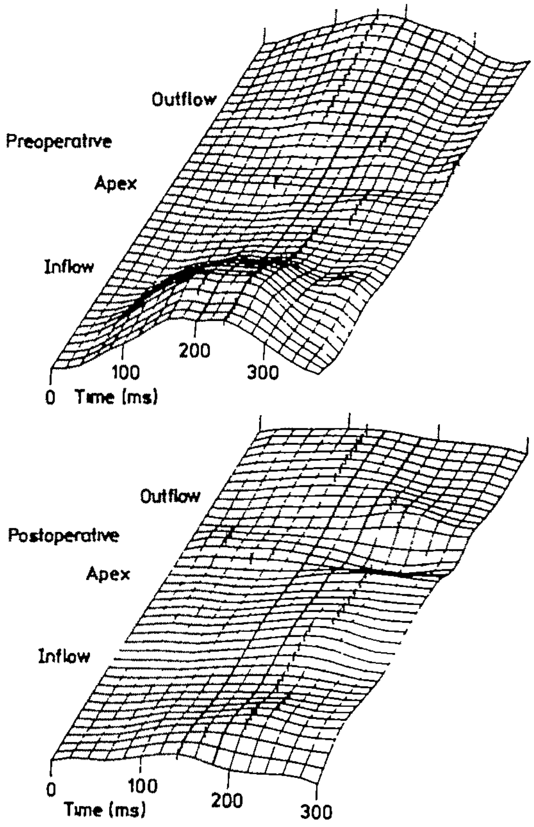


Fig 3 *Right ventricular wall motion plots from a patient before and eight years after a Mustard operation. The overall pattern of motion is similar with outflow tract hypokinesia and an area of apical dyskinesia.*

group as a whole (69 (10)%) and in the two subgroups. The peak ventricular filling rate was much lower in the right ventricle after a Mustard operation (anatomical correction 7·6 (2·0) s), but the RR interval was longer in these patients. When corrected for heart rate the significant difference between the two groups persisted.

The end diastolic shape index measured from the right anterior oblique view was similar in the two groups (anatomical correction 83 (6)%), but the change in shape during systole was less after the Mustard operation (anatomical correction 12·9 (5·1)%), indicating possible differences in the mechanism of ejection in the two groups.

Regional wall motion abnormalities were common after anatomical correction. These were discussed fully in an earlier report.[10] The most common abnormality was anterior hypokinesia, with delay of onset of inward wall motion of the affected segments. This pattern was seen in six of the patients in this study. In two other patients there was inferior hypokinesia and segmental early relaxation during the isovolumic relaxation period, respectively. There was no difference in the frequency of wall motion abnormalities between the two groups.

COMPARISON WITH THE NORMAL AND PRESSURE-LOADED RIGHT VENTRICLE

After the Mustard operation, patients had a higher end diastolic volume, end systolic volume ($p < 0{\cdot}001$), and a lower ejection fraction than controls. The comparison with the unoperated patients with tetralogy of Fallot[12] (when right ventricular pressure is at systemic levels) is perhaps more useful. Again end diastolic and end systolic volumes were higher after a Mustard operation and the ejection fraction was lower. There was no difference in the RR interval between the groups, but the peak filling rate was considerably lower after the Mustard operation.

Discussion

The major concern after intra-atrial repair of transposition of the great arteries is whether the right ventricle can perform adequately as the systemic ventricle throughout life. Anatomical correction restores the left ventricle as the systemic pumping chamber, and now that the high early mortality[18] has improved the central question, in terms of the long term outlook for these patients, is whether left ventricular function after anatomical correction is better than right ventricular function after the Mustard operation?

The most logical approach to answering this question seems to be to compare right ventricular function after the Mustard operation with left ventricular function after anatomical correction. But is this a valid comparison? In the normal heart the right ventricular end diastolic volume is higher, the ejection fraction is lower, and the pressure-volume characteristics are substantially different than those of the left ventricle.[11] Indeed these differences have been highlighted as reasons why it may be invalid to use indices of ventricular function, validated in the left ventricle, to assess right ventricular function.[12] The situation in patients after repair of transposition is somewhat different, however. Under these circumstances, the systemic ventricle (be it a left or right ventricle) is expected to perform the same function. Indeed, results in this study and in others[19 20] show that right ventricular function in some patients after intra-atrial repair may be comparable to that of the normal left ventricle. There must therefore be one basic assumption when the two postoperative groups are compared—that is that under ideal circumstances the right ventricle can perform in the same way as the normal left ventricle.

How does right ventricular function after the Mustard procedure compare with left ventricular function after anatomical correction? The volume of the right ventricle seems to increase after the Mustard procedure to a value that is higher than normal and higher than the pressure-loaded right ventricle. The biggest difference between these groups was in the end systolic volume index, however. This difference was the major determinant of the lower ejection fraction seen after the Mustard operation. Indeed, when compared with the left ventricle after anatomical correction, the ejection fraction was considerably reduced in the Mustard group as a whole, although in eight of the 18 patients the ejection fraction was >55%. Similar results have been reported in previous studies of smaller numbers of patients with simple transposition after intra-atrial repair.[19 20]

Right ventricular shape has not been examined in detail previously. The normal left ventricle becomes progressively less round during systole, and up to 20% of the stroke volume is ejected as a direct consequence of this shape change.[14] This is an efficient mechanism because ejection can occur with less global myocardial fibre shortening, which is an energy consuming process. Our data[10] and that of others[7] showed that this mechanism is preserved in the left ventricle after anatomical correction. After the Mustard operation the end diastolic shape index of the right ventricle was similar to that of the left ventricle after anatomical correction. But the reduction in shape index during systole after the Mustard operation was much less, suggesting that a shape change makes little contribution to right ventricular ejection after the Mustard operation; so this must be almost entirely dependent upon myocardial fibre shortening.

In addition to these differences in systolic function, there was evidence of impairment of diastolic function. The peak rate of right ventricular early diastolic filling after the Mustard operation was less than that of the left ventricle after anatomical correction and that of the right ventricle in tetralogy of Fallot before radical repair. It is possible that this was because the size of the atrial reservoir was reduced by a restrictive intra-atrial baffle. None the less, the filling rates after a Mustard operation were similar to those seen in the right ventricle after repair of tetralogy of Fallot; and a similar mechanism of reduced diastolic compliance, perhaps secondary to diffuse or focal fibrosis, may be invoked.[12] This is important because diastolic abnormalities may relate to abnormalities of the subsequent systole. The strong correlation between peak filling rate and ejection fraction in this study supports this concept and accords with the work of Sideris *et al* who showed a similar relation between right ventricular diastolic and systolic function in these patients.[21]

There was no relation between any of these indices and age at operation or time from operation in either of the two groups. Others reported this lack of correlation between length of time from operation and impairment of ventricular function[22] and in a recently published longitudinal study there was no deterioration in ejection fraction measured over a five year period.[23] If the impairment of right ventricular function after the Mustard operation is caused by the long term effects of increased afterload,[24] this is somewhat surprising. It is possible that preoperative and operative factors are more important in determining postoperative function. Boucek *et al* reported that concentrations of creatine kinase MB isoenzyme were high before operation.[25] In another study the preoperative right ventricular ejection fraction was low.[24]

Half of our patients had abnormal wall motion plots. Furthermore, when the group of patients with abnormal plots was compared with a group with no gross abnormalities, those with abnormal plots had a lower right ventricular ejection fraction and peak ventricular filling rate. These observations are supported by data from a cross sectional echocardiographic study showing dyskinetic right ventricular wall movement in three patients with congestive heart failure but not in others who were clinically well after the Mustard operation.[26]

Even more important, perhaps, was the finding that four of the five patients in whom an appropriate preoperative right ventriculogram was available showed an abnormal dyskinetic pattern of right ventricular wall motion before operation and in three of these four patients the preoperative wall motion plots were similar. Further longitudinal studies are required but it seems that preoperative and operative factors may be important in determining postoperative function, there being little evidence of deterioration with time in these patients.

The clinical importance of these data is less clear. While the finding of ejection fractions of <40% in six of our 18 patients is worrying, all of the patients were symptom free and leading normal lives. It is possible that deterioration in function will become manifest as follow up in these patients lengthens, and it must be recognised that these patients represent a highly selected group. Global left ventricular function is well preserved early after anatomical correction, as shown by our own and other data, but wall motion abnormalities are common. However, follow up in this group of patients is even shorter than that for those who had a Mustard operation and the significance of these abnormalities and the possible long term effects of right ventricular outflow tract obstruction[13] and aortic regurgitation,[27] which are becoming increasingly recognised, are unknown. The selection of the appropriate operation in the individual patient remains difficult. It may be that formal assessment of right and left ventricular function before operation will enable more appropriate selection.

We thank Dr David Hughes and Mrs Susan Jones for their help in undertaking this study.

References

1 Trusler GA, Mustard WT. Palliative and reparative procedures for transposition of the great arteries. *Ann Thorac Surg* 1974;**17**:410–21.

2 Jatene AD, Foutes VF, Paulista PP, *et al.* Anatomic correction of transposition of the great vessels. *J Thorac Cardiovasc Surg* 1976;**72**:364–70.

3 Mahony L, Turley K, Ebert P, Heyman MA. Long-term results after atrial repair of transposition of the great arteries in early infancy. *Circulation* 1982;**66**: 253–7.

4 Arciniegas E, Farooki ZQ, Hakimi M, Perry BL, Gree EW. Results of the Mustard operation for dextro-transposition of the great arteries. *J Thorac Cardiovasc Surg* 1981;**81**:580–5.

5 Graham TP, Atwood GF, Boucek RJ, Boerth RC, Bender HW. Abnormalities of right ventricular function following Mustard's operation for transposition of the great arteries. *Circulation* 1975;**52**:678–84.

6 Mee RBB. Severe right ventricular failure after Mustard or Senning operation. *J Thorac Cardiovasc Surg* 1986;**92**:385–90.

7 Arensman FW, Radley-Smith R, Yacoub MH, *et al.* Catheter evaluation of left ventricular shape and function one or more years after anatomic correction of transposition of the great arteries. *Am J Cardiol* 1983;**52**.1079–83.

8 Sievers HH, Lange PE, Onnasch DGW, *et al.* Influence of the two-stage anatomic correction of simple transposition of the great arteries on left ventricular function. *Am J Cardiol* 1985;**56** 514–9.

9 Borow KM, Arensman FW, Webb C, Radley-Smith R, Yacoub MH. Assessment of left ventricular contractile state after anatomic correction of transposition of the great arteries. *Circulation* 1984;**69**:106–12.

10 Lincoln C, Redington AN, Li K, Mattos S, Shinebourne EA, Rigby ML. Anatomical correction for complete transposition and double outlet right ventricle: intermediate assessment of functional results. *Br Heart J* 1986;**56**:259–66.

11 Redington AN, Gray HH, Hodson ME, Rigby ML, Oldershaw RJ. Characterisation of the normal right ventricular pressure-volume relation by biplane angiography and simultaneous micromanometer pressure measurements. *Br Heart J* 1988;**59**:23–30.

12 Redington AN, Oldershaw RJ, Shinebourne EA, Rigby ML. A new technique for the assessment of pulmonary regurgitation and its application to the assessment of right ventricular function before and after repair of tetralogy of Fallot. *Br Heart J* 1988;**60**: 57–65.

13 Carvalho JS, Shinebourne EA, Busst CM, *et al.* Haemodynamic findings in asymptomatic children 10 years after Mustard's operation for transposition of the great arteries. *Int J Cardiol* (in press).

14 Gibson DG, Brown DJ Continuous assessment of left ventricular shape in man. *Br Heart J* 1975;**37**:904–10.

15 Gibson DG, Fleck E, Rudolph W. Effect of postextrasystolic potentiation on amplitude and timing of regional left ventricular wall motion in ischaemic heart disease. *Br Heart J* 1983;**49**.466–76.

16 Hui WKK, Gibson DG. Mechanisms of reduced ventricular filling rate in coronary artery disease. *Br Heart J* 1983;**50**:362–71.

17 Gibson DG, Mehmel H, Schwarz F, Li K, Kubler W. Asynchronous left ventricular wall motion early after coronary thrombosis. *Br Heart J* 1986;**55**:4–13.

18 Bical O, Hazan E, LeCompte Y, *et al.* Anatomic correction of transposition of the great arteries associated with ventricular septal defect: midterm results in 50 patients. *Circulation* 1984;**70**:891–7.

19 Okuda H, Nakazawa M, Imai Y, *et al.* Comparison of ventricular function after Senning and Jatene procedures for complete tansposition of the great arteries. *Am J Cardiol* 1985;**55**:530–4.

20 Graham TP, Burger J, Bender HW, Hammon JW, Boucek RJ, Appleton S. Improved right ventricular function after intra-atrial repair of transposition of the great arteries. *Circulation* 1985;**72**(suppl II): 45–51

21 Sideris EB, Olley PM, Spooner E, Farina M, Shaher R. Ventricular pressure-volume relations after the intra-atrial baffle operation for transposition of the great arteries *Am Heart J* 1982;**104**.1045–53.

22 Hagler DJ, Ritter DG, Mair DD, *et al.* Right and left ventricular function after the Mustard procedure for transposition of the great arteries. *Am J Cardiol* 1979; **44**:276–83.

23 Wong KY, Venables AW, Kelly MJ, Kalff V. Longitudinal study of ventricular function after the Mustard operation for transposition of the great arteries: a long term follow-up. *Br Heart J* 1988; **60**:316–23.

24 Jaymakani JMM, Canent RV. Preoperative and postoperative right ventricular function in children with transposition of the great arteries. *Circulation* 1974; **50**(suppl II):39–45.

25 Boucek RJ, Kasselberg AG, Boerth RC, Parrish MD, Graham TP Myocardial injury in infants with congenital heart disease· evaluation by creatine kinase MB isoenzyme analysis. *Am J Cardiol* 1982;**50**: 129–34.

26 Trowitczsch E, Colan SD, Sanders SP. Global and regional right ventricular function in normal infants and infants with transposition of the great arteries after Senning operation. *Circulation* 1985;**72**: 1008–14.

27 Helgason H, Hougen TJ, Jacobs M, *et al.* Hemodynamic results of primary anatomic repair of transposition of the great arteries. Transactions of the 22nd World Congress of Paediatric Cardiology 1985

Br Heart J 1989;62:462–6

Cardiac involvement in Churg-Strauss syndrome shown by echocardiography

J M MORGAN, L RAPOSO, D G GIBSON

From the Cardiac Department, Brompton Hospital, London

SUMMARY To define the range of cardiac involvement in the Churg-Strauss syndrome, M mode, continuous wave Doppler, and cross sectional echocardiograms were recorded in twelve patients with the disorder. The M mode recordings were digitised and the cross sectional images were recorded with standardised gain settings to determine regional myocardial echo amplitude. Left ventricular end diastolic and end systolic dimensions were increased above the normal 95% confidence interval in four patients, three of whom showed a depressed shortening fraction. Mitral regurgitation was present in six patients; this was severe enough to need valve replacement in two. Mean echo amplitude in both the septum and the posterior wall was significantly increased above normal by a mean (SD) of 4·87 (2·57) dB, suggesting the presence of myocardial fibrosis. There was no evidence of subendocardial involvement as there is in other hypereosinophilic syndromes.

Mitral regurgitation is common in the Churg-Strauss syndrome. This cannot be ascribed to involvement of the cusps or chordae and it occurs even when ventricular function is well preserved. It is suggested that mitral regurgitation is caused by diffuse myocardial fibrosis.

The Churg-Strauss syndrome is recognised by the combination of blood eosinophilia, eosinophilic tissue infiltration, extravascular fibrinoid necrotising (allergic) epithelioid and eosinophilic granuloma formation, and disseminated necrotising vasculitis occurring in asthmatic patients.[1 2] Lanham *et al* noted that "the histological components of the syndrome often do not coexist temporally or spatially" and suggested that the clinical pattern of a prodromal phase of allergic disease, followed by a second phase characterised by eosinophilic tissue infiltration and peripheral blood eosinophilia culminating in a third vasculitic phase, should supercede strict adherence to histopathological criteria for the purposes of diagnosis.[3] Myocardial fibrosis, particularly in the subendocardial region, is a characteristic feature of the idiopathic hypereosinophilic syndrome[4] and it has been attributed directly to the eosinophilia itself. Possible cardiac involvement in patients with Churg-Strauss syndrome and comparable blood eosinophilia, however, is less well defined. We therefore studied a series of patients with Churg-Strauss syndrome by M mode, continuous wave Doppler, and cross sectional echocardiography to assess whether they were also at risk for heart disease.

Requests for reprints to Dr J M Morgan, National Heart Hospital, London W1M 8BA

Accepted for publication 6 April 1989

Patients and methods

We studied 12 patients in whom the diagnosis of Churg-Strauss syndrome was made on the basis of histological criteria[1 2] and clinical features.[3] The blood eosinophil count was raised in all (eosinophil counts ranged from 2·3 to 11 × 10^9 l at presentation). The results of echocardiography were compared with those in 20 age and sex matched controls with no clinical evidence of heart disease in whom stress test had been negative at high workload.

ECHOCARDIOGRAPHY

Cross sectional echocardiograms were recorded in parasternal views. The regional echo amplitude was displayed in real time by a Brompton encoder.[5] The master gain setting of the echocardiograph was standardised as the lowest level at which the parietal pericardium behind the posterior left ventricular wall appeared as a continuous line at the highest level of pixel intensity (white on the display), and the depth compensation was adjusted to give linear change across the image. Echocardiographic images were recorded on 3/4 inch tape by a Sony U-matic recorder for further study.

End diastolic stop frame images were subsequently displayed by a tape recorder with digital frame advance (Sony 5800 PS). Four areas of interest were identified: mid and basal septum and mid and basal posterior wall. We took care to limit sampling to these areas on the myocardium itself and to avoid specular echoes from the endocardium or epicardium. In each region approximately 300 pixels were included within the area of interest. From each the distribution of pixel intensity in each of the 64 grey scale levels was displayed as a histogram, and printed separately. Mean and median pixel levels for each region were calculated.

M mode echocardiograms were recorded under cross sectional control from the level of the tips of the mitral leaflets at a paper speed of 100 m/s with a simultaneous phonocardiogram and electrocardiogram. They showed clear, continuous echoes from the left side of the septum and the endocardial surface of the posterior wall.

M mode echocardiograms were digitised,[6] and the following measurements were made: (*a*) maximum and minimum cavity diameter; (*b*) fractional shortening; (*c*) septal and posterior wall thickness; (*d*) percentage increase in posterior wall thickness during systole; (*e*) peak rate of change of cavity dimension during systole and diastole; and (*f*) peak rate of change of posterior wall thickness during systole and diastole.

Continuous wave Doppler cardiograms were recorded from the apex with a Doptek Spectrascan along with a simultaneous phonocardiogram and electrocardiogram. The aim was to detect the presence or absence or the typical flow-velocity signal of mitral regurgitation. If it was present, we noted the time that it stopped in relation to the onset of the aortic component of the second heart sound (fig 1).[7]

Table 1 *Left ventricular cavity size and fractional shortening in patients with mitral regurgitation*

Patient	*LV-ED-dim*	*LV-ES-dim*	*%FS*	*Duration MR (ms)*
1	6·3	5·4	15	100
2*	7·4	6·1	18	40
3	6·5	6	8·4	90
4*	6·2	4	35	N/A
5	5·3	3	44	N/A
6	5	3·1	44	90
	3·5–5·5 (95% confidence interval)	2·1–3·7	25–47	

*Later underwent mitral valve replacement. N/A, not available; LV-ED-dim, left ventricular end diastolic cavity dimension (cm); LV-ES-dim, left ventricular end systolic dimension (cm); %FS, percentage fractional shortening, MR; mitral regurgitation after aortic valve closure.

STATISTICAL ANALYSIS

We compared results of M mode digitisation and myocardial echo amplitude estimates in the patients with Churg-Strauss syndrome with 95% confidence intervals for normal controls. Student's *t* test was used to determine statistical significance.

Results

CONTINUOUS WAVE DOPPLER

Mitral regurgitation was recorded by continuous wave Doppler in six of twelve patients. In four it was judged to be mild on clinical and haemodynamic grounds, and in three of these the regurgitation persisted for more than 50 ms after the aortic component of the second heart sound. In the fourth the measurement could not be made because A_2 was not adequately defined on the phonocardiogram. In one of the two remaining patients with mitral regurgitation severe enough to require valve replacement the corresponding interval was 40 ms while in the other A_2 was again undefined (table 1).

Overall, there was no significant difference between the patients and controls subjects in any of the measurements made from the digitised M modes. However, the left ventricular cavity dimension and fractional shortening were outside the 95% confidence intervals for normal in four of the six patients with mitral regurgitation (table 1). In two of the four in whom regurgitation was mild, fractional shortening was also reduced. In the other two patients, however, cavity dimensions and fractional shortening were normal. Cavity dimensions were increased in both the patients with severe regurgitation, fractional shortening being reduced in one and normal in the other. Thus in three of the six patients with mitral regurgitation, fractional shortening was well preserved.

MYOCARDIAL ECHO AMPLITUDE

Mean myocardial echo amplitude in all twelve patients studied was outside the 95% confidence intervals for the controls in each of the four regions of myocardium (table 2). Overall, echo amplitude in

Table 2 *Myocardial echo amplitude in patients with Churg-Strauss syndrome and controls*

Group	*MPW (SD)*	*BPW (SD) (dB)*	*MS (SD) (dB)*	*BS (SD)*
Churg-Strauss	*10·5 (3·09)	*8·02 (2·47)	*9·03 (3·09)	*6·94 (2·99)
Controls	3·51 (0·32)	3·42 (0·36)	4·59 (0·36)	3·5 (0·32)

*$p < 0·001$, compared with controls; measurements in decibels. MPW, mid posterior wall; BPW, basal posterior wall, MS, mid septum; BS, basal septum

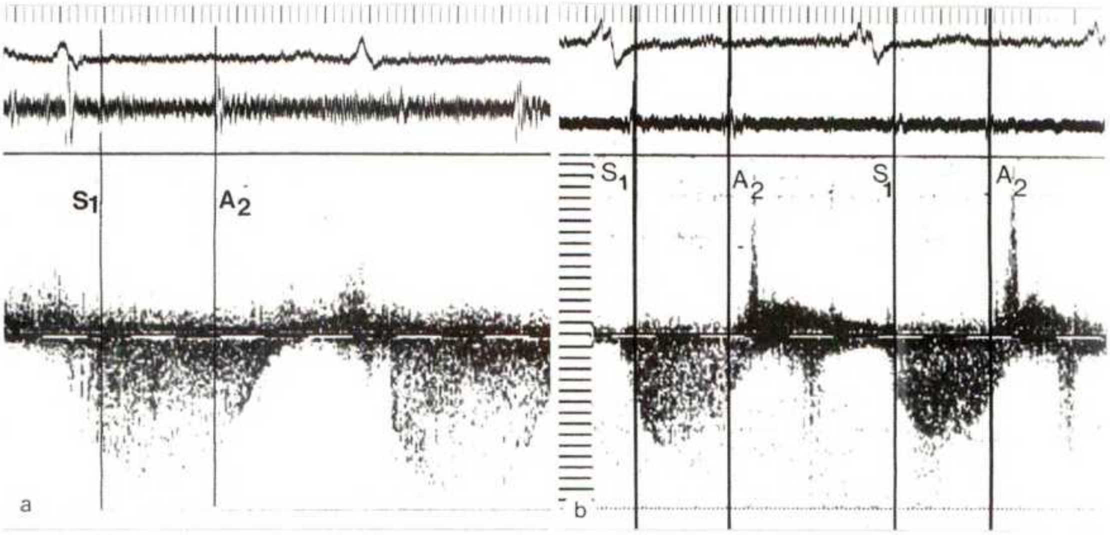


Fig 1 *Velocity profile from continuous wave Doppler traces showing (a) mild mitral regurgitation and (b) severe mitral regurgitation and their relation of the end of mitral regurgitation to the aortic component of the second heart sound on the phonocardiogram (paper speed 100 mm/s; 16 kHz scale). A_2, aortic component of second heart sound.*

patients with the Churg-Strauss syndrome was increased above normal by a mean of 4·87 (2·57) dB ($p < 0·001$) in both septum and the posterior wall. Subsequent echocardiography showed that this increase persisted, so that it is unlikely to have been caused by myocarditis at the time of diagnosis.

Inspection of the colour encoded images showed no regional increase in echo amplitude (fig 2). In

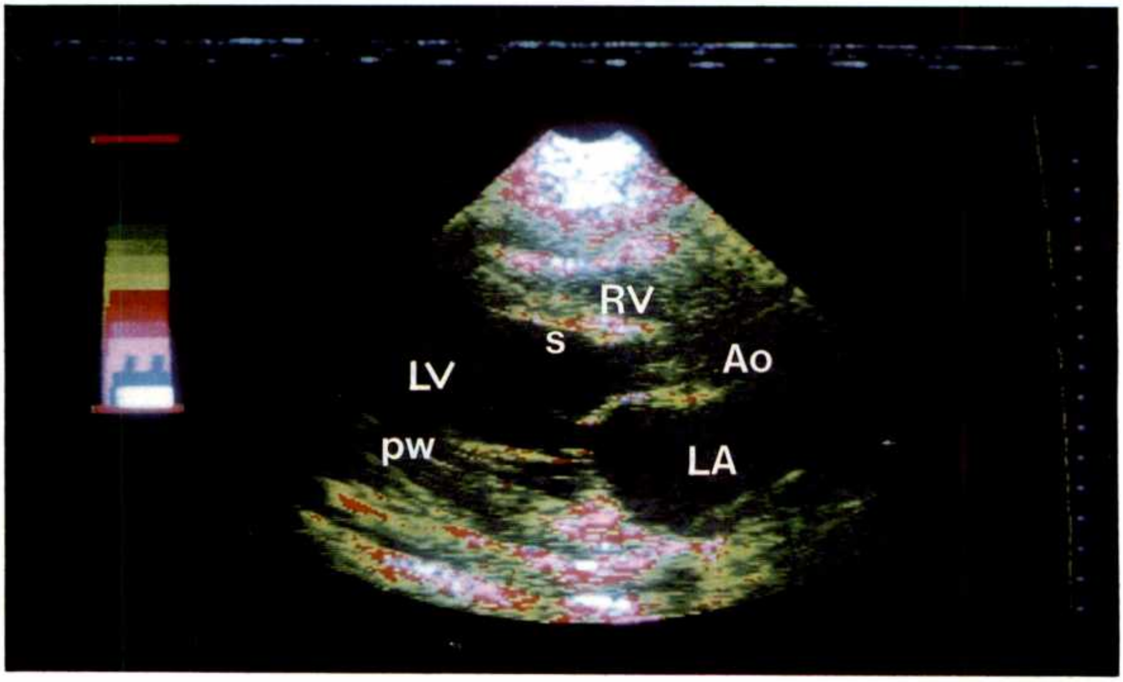


Fig 2 *Parasternal long axis view, processed image, showing generalised increase in myocardial echo amplitude. RV, right ventricle; LV, left ventricle; LA, left atrium; Ao, aortic root; PW, posterior left ventricular wall; S, interventricular septum. Highest level of pixel intensity is white (see scale).*

addition, there was no significant difference in amplitude between any of the four sites sampled in the patients, indicating that the distribution of the increase was generalised rather than localised.

Discussion

The relation between blood eosinophilia and heart disease is well recognised.[4 8 9] Endomyocardial fibrosis is prominent in the hypereosinophilic syndrome and leads to a characteristic clinical picture of restrictive cardiomyopathy accompanied by atrioventricular valve regurgitation when the papillary muscles are affected.[4 10] There is much evidence to suggest that these cardiac abnormalities are the direct result of eosinophilia and that they persist even if the eosinophilia itself has subsided.[4 11] Thus Chew *et al* reported eleven cases of subendocardial fibrosis in patients presenting with restrictive cardiomyopathy, although in only two was there documented eosinophilia.[12]

The Churg-Strauss syndrome is distinguished from other causes of hypereosinophilia by specific clinical and histopathological features. Asthma is common but, unlike polyarteritis nodosa, renal involvement is unusual.[2 3] Histologically a disseminated necrotising vasculitis affects the small arteries and veins, together with necrotising (allergic) epithelioid and eosinophilia granulomas. Despite the frequent occurrence of eosinophilia, the possibility that clinically significant heart disease might occur in the Churg-Strauss syndrome has received little attention in published reports, even in the original description of cardiac involvement[1] and was not considered in the large series reported by Chumbley *et al*,[2] despite the frequency of heart disease at necropsy.

More recently, Spry *et al* noted the presence of diffuse myocardial fibrosis in Churg-Strauss syndrome[13] and extensive replacement of the myocardium by granulomas and scar tissue has been reported.[14] Furthermore, Lanham *et al* noted that cardiac involvement accounted for death in 48% of patients with the condition.[3] Davison *et al* also drew attention to cardiac disease in three patients (included in our series), two of whom had evidence of pericardial involvement and one with additional myocardial disease.[15] It was for this reason that the present, more comprehensive investigation was undertaken, by non-invasive methods that have proved effective in detecting cardiac involvement in other forms of heart disease associated with hypereosinophilia. Regional echo amplitude has previously been shown to correlate with myocardial collagen content in chronic heart disease.[16] The method has been used to show localised fibrosis in patients with tropical endomyocardial disease and in endomyocardial fibrosis,[17 18] especially when it affects the subendocardium and papillary muscles. We found an increase in myocardial echo amplitude in all the patients we studied. But this differed from what we saw in other patients with hypereosinophilia in having a generalised distribution. Theoretically, it might have been caused by myocardial oedema, which we have previously shown to be a cause of increased myocardial echo intensity when it is associated with acute rejection in the transplanted heart.[19] We think that this is an unlikely cause in the present patients, however, because the increased echo intensities persisted when other acute manifestations of the disease, such as eosinophilia, asthma, and vasculitis, had subsided. We cannot confirm this theory by histology in our patients, because none of them has died and endomyocardial biopsy in one patient yielded an inadequate sample. Nevertheless, we conclude that the increase in myocardial echo intensity reflects the generalised increase in myocardial collagen content as found in previous histological studies.

We were also able to study the effects of this fibrosis on left ventricular function. The results of M mode digitisation suggested that simple measurements of systolic and diastolic performance were well preserved. Unlike the hypereosinophilic syndrome,[8] there was no echocardiographic evidence that the valve cusps were affected. Nevertheless, continuous wave Doppler detected the presence of mitral regurgitation in six of the twelve patients, an unexpectedly high frequency. In two of these patients it was severe enough to require mitral valve replacement, and in two of the remaining four, in whom it was mild, left ventricular cavity size was not increased. It was not possible, therefore, to attribute this regurgitation simply to cavity dilatation. We suggest, rather, that it is the direct consequence of fibrosis of the papillary muscles occurring as part of the more generalised myocardial effects seen in this disease.

We conclude, therefore, that myocardial fibrosis of generalised distribution is a notable, though usually subclinical feature of the Churg-Strauss syndrome. It may result in left ventricular disease or, more characteristically, in mitral regurgitation which is more severe, and which may occur at a smaller cavity size than that seen in association with other types of left ventricular disease. We believe that echocardiography should be performed on all cases of the syndrome to document the presence and extent of heart disease, because in some it may play a prominent part in the clinical manifestations of the condition.

We thank Dr A Newman-Taylor, Professor M Turner-Warwick, Dr D Geddes, and Professor P Barnes for allowing us to investigate their patients.

References

1 Churg J, Strauss L. Allergic granulomatosis, vasculitic angiitis and periarteritis nodosa. *Am J Pathol* 1951;**27**:227–310.

2 Chumbley LC, Harrison EG, De Reinee RA. Allergic granulomatosis and angitis (Churg Strauss syndrome). *Mayo Clin Proc* 1977;**52**:477–81.

3 Lanham JG, Elkon KB, Pusey CD, Hughes GR. Systemic vasculitis with asthma and eosinophilia: a clinical approach to the Churg Strauss syndrome. *Medicine (Baltimore)* 1984;**63**:65–81.

4 Oakley CM, Olsen EGJ. Eosinophilia and heart disease. *Br Heart J* 1977;**39**:233–7.

5 Logan-Sinclair R, Wong CM, Gibson DG. Clinical application of amplitude processing of echocardiographic images. *Br Heart J* 1981;**45**:621–7.

6 Upton MT, Gibson DG. The study of left ventricular function from digitised echocardiograms. *Prog Cardiovasc Dis* 1978;**20**:359–84.

7 Bradley JA, Gibson DG. Assessment of the severity of mitral regurgitation from the dynamics of retrograde flow. *Br Heart J* 1988;**60**:134–40.

8 Roberts WC, Liegler DG, Carbone PP. Endomyocardial disease and eosinophilia. A clinical and pathological spectrum. *Am J Med* 1969;**46**:28–42.

9 Olsen EGJ, Spry CJF. Relationship between eosinophilia and endomyocardial disease. *Prog Cardiovasc Dis* 1985;**27**:241–54.

10 Chusid MJ, Dale DC, West BC, Wolff SM. The hypereosinophilic syndrome: analysis of fourteen cases with review of the literature. *Medicine (Baltimore)* 1975;**54**:1–27.

11 Roberts WC, Buja LM, Ferrans VJ. Loefflers fibroplastic parietal endocarditis, eosinophilic leukaemia and Davies' endomyocardial fibrosis: the same disease at different stages? *Pathologia et Microbiologia* 1970;**35**:90–5.

12 Chew CYC, Ziady GM, Raphael MJ, Nellen M, Oakley CM. Primary restrictive cardiomyopathy: non-tropical endomyocardial fibrosis and hypereosinophilic heart disease. *Br Heart J* 1977;**39**:399–413.

13 Spry CJF, Take M, Tai P-C. Eosinophilic disorders affecting the myocardium and endocardium: a review. *Heart and Vessels* 1985;suppl I:240–2.

14 Rosenberg TF, Medsger TA, DeCicco FA, Fireman P. Allergic granulomatosis angiitis (Churg-Strauss syndrome). *J Allergy Clin Immunol* 1975;**55**:56–9.

15 Davison AG, Thompson PJ, Davies J, Corrin B, Turner-Warwick M. Churg-Strauss syndrome (allergic granulomatosis and angitiis). *Thorax* 1983;**38**:793–5.

16 Shaw TRD, Logan-Sinclair RB, Surin C, *et al.* Relation between regional echo intensity and myocardial connective tissue in chronic left ventricular disease. *Br Heart J* 1984;**51**:46–53.

17 Vijayaraghavan G, Davies J, Sadanandan S, Spry CJF, Gibson DG, Goodwin JF. Echocardiographic features of tropical endomyocardial disease in South India. *Br Heart J* 1983;**50**:450–9.

18 Davies J, Gibson DG, Foale R, *et al.* Echocardiographic features of eosinophilic endomyocardial disease. *Br Heart J* 1982;**48**:434–40.

19 Swanson KT, Greenbaum RA, Logan-Sinclair RB, Gibson DG, Yacoub MH. Quantitative echocardiographic tissue characterisation after cardiac transplantation [Abstract]. *Br Heart J* 1988;**59**:629.

Br Heart J 1989;**62**:467–9

Case reports

Potential value of intraoperative Doppler colour flow mapping in operations for complex intracardiac shunting

G R SUTHERLAND, S BALAJI, J L MONRO

From the Department of Paediatric Cardiology, Wessex Cardiothoracic Unit, Southampton General Hospital, Southampton

SUMMARY An eight year old boy presented with multiple residual intracardiac shunts and considerable persisting haemolytic anaemia five years after the repair of a single perimembranous ventricular septal defect. Preoperative transthoracic colour flow mapping showed an "acquired" left ventricular right atrial shunt and three small residual ventricular septal defects around the patch. These had been poorly visualised by both angiography and conventional cross sectional echocardiography and pulsed and continuous wave Doppler. Clearly, to stop the haemolysis effectively, closure of all residual intracardiac shunts was required. Intraoperative pre-bypass colour flow mapping was successfully used to confirm the precise number and nature of the defects and more importantly studies after bypass were used to confirm immediate closure of all defects.

There can be major diagnostic problems when multiple complex intracardiac shunts are present. The information provided by angiography is often inadequate. Cross sectional echocardiography with integrated colour flow mapping can reliably define the origin and extent of such complex disturbances.[1-3] We report a case that shows the unique diagnostic advantages of the technique, but more importantly we describe its intraoperative use in confirming the closure of multiple defects, one or more of which were causing severe haemolysis.

Case report

An eight year old boy was referred five years after attempted surgical repair of a single perimembranous ventricular septal defect with a concomitant aortic valvotomy. Considerable haemolytic anaemia had been noted during the fifth postoperative month. Clinical examination suggested a small residual ventricular septal defect. Treatment with iron and folic acid supplements was started. Over the next four years his haemoglobin concentration remained normal but a reticulocytosis of 20% persisted.

On admission, examination showed signs of a residual ventricular septal defect and mild aortic stenosis. Duplex scanning (imaging + pulsed and continuous wave Doppler) suggested only a single ventricular septal defect at the subaortic end of the patch (transseptal peak jet velocity of 5 m/s). Colour flow mapping showed numerous residual discrete jets—one from the left ventricle to right atrium ("acquired" Gerbode type defect) and three peri-patch transseptal jets from the left to right ventricle. Subsequent left ventricular angiography from appropriately angled views suggested only two ventricular septal defects but failed to show the "acquired" Gerbode defect.

Successful surgical closure of all defects was clearly essential to stop the haemolytic anaemia. We decided to carry out "intraoperative angiography" using colour flow mapping to confirm the sites of the defects and to confirm defect closure. Intraoperative

Requests for reprints to Dr G R Sutherland, Department of Cardiac Ultrasound, Thoraxcenter, Ba 300, Erasmus University, 3000 DR Rotterdam, The Netherlands

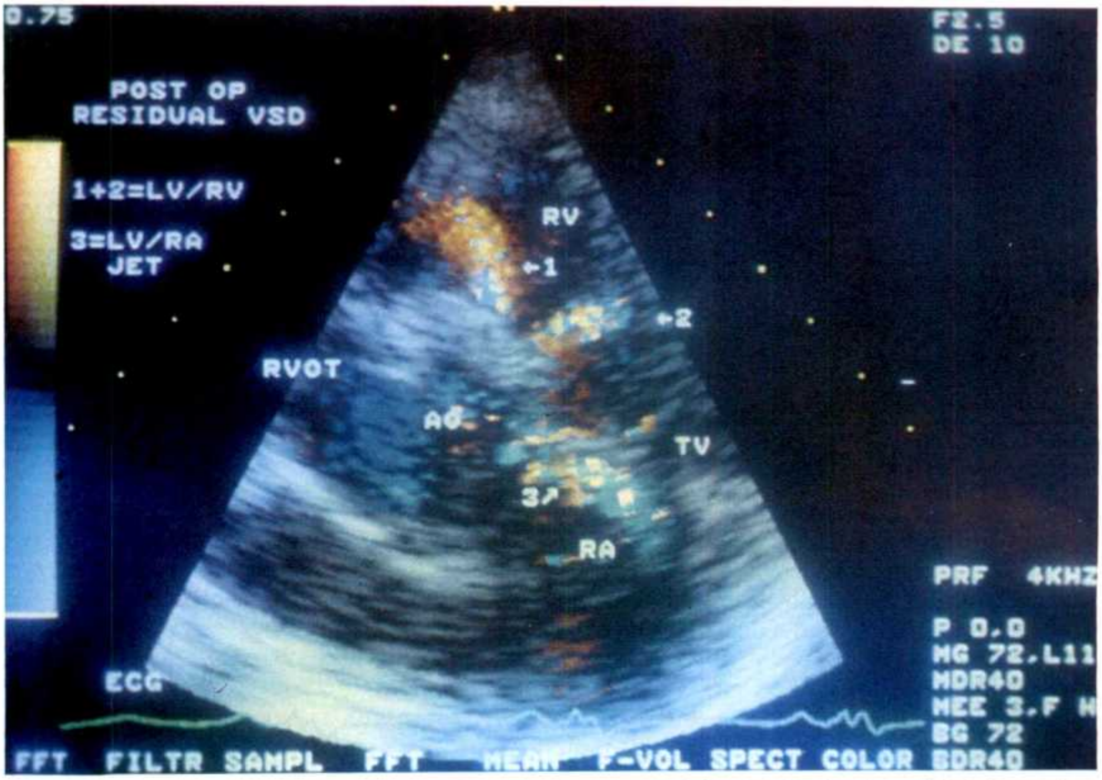


Fig 1 *Intraoperative pre-repair colour flow map in the short axis, right ventricular view showing three residual intracardiac shunts. Numbers 1 and 2 are interventricular shunts and 3 is a left ventricle to right atrial shunt (a further more apical ventricular septal defect was present at the lower end of the patch that could not be included in this view). Blood flow towards the transducer is red and flow away from the transducer is blue. Turbulence (that is a high velocity flow disturbance) is encoded as a mosaic of yellow. RA, right atrium; RV, right ventricle; RVOT, right ventricular outflow tract; Ao, aorta; LV, left ventricle.*

colour flow mapping was performed with a Toshiba SSH-65A. The transducers (5 MHz for imaging, and 2·5 MHz for colour flow mapping) were placed into long (2 metre) sterile plastic bags containing ultrasound gel which were then placed directly on the beating heart. Intraoperative colour flow mapping confirmed the presence of the "acquired" Gerbode defect and showed three further restrictive ventricular septal defects all around the margins of the patch (fig 1). All defects were then closed with Teflon pledgets. Epicardial colour flow mapping was repeated with the patient off cardiopulmonary bypass. This showed normal low velocity laminar flow within the right heart with no residual turbulence in either right atrium or right ventricle (fig 2). A transthoracic colour flow mapping study on the fifth postoperative day confirmed the continuing integrity of the repair.

Six months after operation further colour flow mapping studies showed no residual septal defect. Since operation both the haemoglobin concentration and reticulocyte count have remained normal.

Discussion

It was important in this patient to identify all the residual defects before operation and then to confirm successful surgical closure intraoperatively because any or all of the defects could have contributed to the haemolysis. In this patient intraoperative epicardial colour flow mapping proved to be more sensitive than either duplex scanning or angiography in the preoperative assessment. Intraoperative colour flow mapping proved to be easy to perform, sensitive, and provided a rapid guide to the surgeon as to the site of the residual defects and the subsequent adequacy of his repair. This case shows the great value of this technique in the management of patients with multiple complex intracardiac shunts.

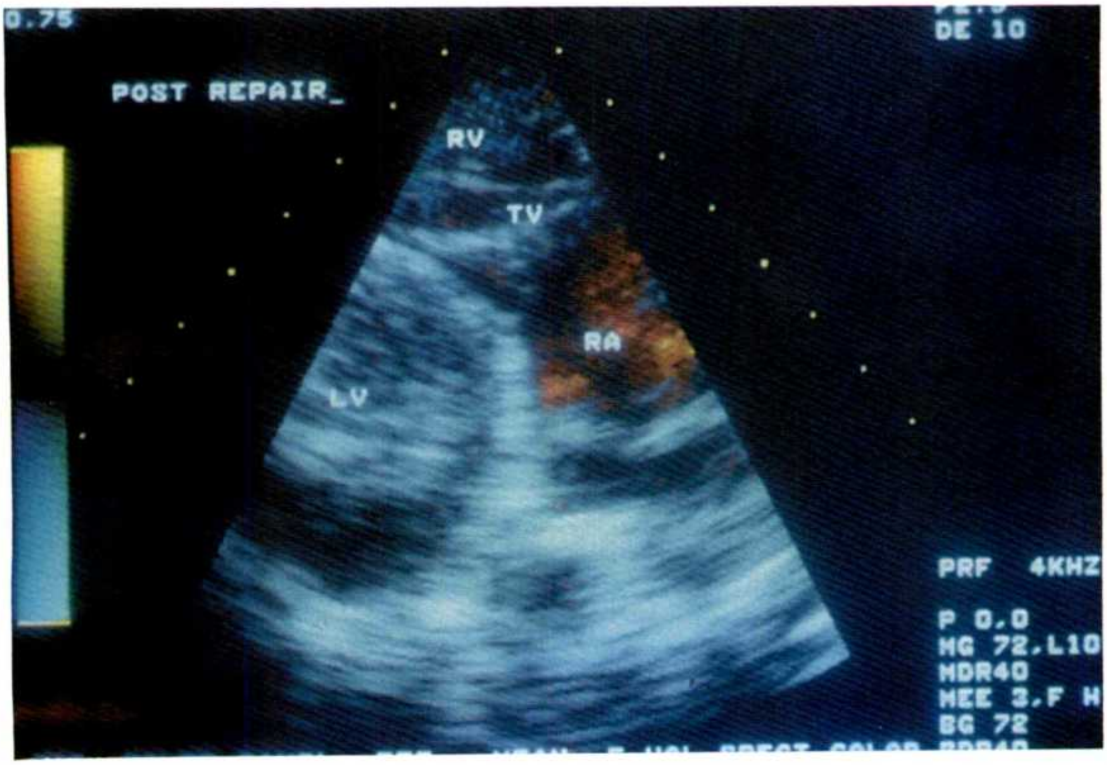


Fig 2 *Foreshortened four chamber view of intraoperative post-repair colour flow map showing no residual turbulent flow within either the right ventricle or right atrium. No residual intracardiac shunts. The left ventricle cavity is small because of hypovolaemia immediately after the patient came off cardiopulmonary bypass. See legend to fig 1 for abbreviations.*

References

1 Takamoto S, Kyo S, Adachi H, *et al.* Intraoperative colour flow mapping by real-time two-dimensional Doppler echocardiography for evaluation of valvular and congenital heart disease and vascular disease. *J Thorac Cardiovasc Surg* 1985;**90**:802–12.

2 Ortiz E, Robinson PJ, Deanfield JE, Franklin R, Macartney FJ, Wyse RKH. Localisation of ventricular septal defects by simultaneous display of superimposed colour Doppler and cross sectional echocardiographic images. *Br Heart J* 1985;**54**:53–60.

3 Ludomirsky A, Huhta JC, Vick GW, Murphy DJ, Danford DA, Morrow WR. Colour Doppler detection of multiple ventricular septal defects. *Circulation* 1986;**74**:1317–22.

Br Heart J 1989;62:470–4

Unusual and intraoperative epicardial echocardiographic features of a papillary tumour of the aortic valve

NEIL P LEWIS, GERAINT T WILLIAMS,* ALAN G FRASER

*From the Departments of Cardiology and *Pathology, University Hospital of Wales, Heath Park, Cardiff*

SUMMARY A mass with a diameter of 0·8 cm was detected in the aortic root of a 53 year old woman during routine preoperative cross sectional echocardiographic assessment of a secundum atrial septal defect. Intraoperative epicardial echocardiography showed that the mass was attached by a slender stalk to the tip of the left coronary cusp of the aortic valve, and histological examination showed that it was a papillary tumour.

Intraoperative epicardial echocardiography can help in planning the excision of papillary tumours, and excision is advised even when there are no symptoms.

Papillary tumours of the heart are uncommon. Until recently, they were diagnosed only as an incidental finding at necropsy,[1] but now they can be detected more frequently by cross sectional echocardiography[2] or recognised during cardiac operation.[3] The aetiology of papillary tumours is uncertain. These lesions are not always asymptomatic and they need to be diagnosed accurately and distinguished from other conditions such as vegetations caused by infective endocarditis, which are managed differently.

There has been only one previous report of the cross sectional echocardiographic diagnosis of a papillary tumour arising from the aortic valve[4]; in another patient who had M mode echocardiography alone, the features were thought to suggest infective endocarditis and the diagnosis was not established until operation.[5] We describe the preoperative and intraoperative epicardial echocardiographic features of a papillary tumour of the aortic valve.

Case report

A 53 year old woman reported dyspnoea on exertion for two years. She had no other symptoms, and in particular no history of chest pain or episodes suggestive of systemic embolism. On examination, the pulse was regular and the blood pressure and venous pressure were normal. There was a mild parasternal lift, fixed splitting of the second heart sound, and an ejection systolic murmur over the pulmonary area.

The electrocardiogram showed sinus rhythm, complete right bundle branch block, and a normal cardiac axis. The chest radiograph showed mild cardiomegaly, an enlarged main pulmonary artery, and pulmonary plethora. Routine haematological and biochemical tests and urine analysis and culture were normal. Blood cultures yielded no growth. The erythrocyte sedimentation rate was 13 mm in the first hour.

Echocardiography was performed with a Hewlett Packard duplex system. The right ventricle was enlarged (diastolic and systolic dimensions from M mode 3·7 and 2 9 cm) and there was paradoxical motion of the interventricular septum. Cross sectional imaging showed an ostium secundum atrial septal defect, and a mass in the aortic root that was featureless, round, and 0·8 cm in diameter (area 1·5 cm^2). It was seen well in both parasternal long axis and short axis planes, in the region of the commissure between the right and left coronary cusps of the aortic valve (fig 1a,b). The mass was not apparent on most M mode recordings of the aortic valve. There was no aortic regurgitation. The mass was thought to be a myxoma, although a vegetation (and thus infective endocarditis) could not be excluded.

Cardiac catheterisation also confirmed that the patient had an atrial septal defect. The pulmonary to systemic flow ratio was 3:1, and the pulmonary artery pressure was 50/15 mm Hg. Neither left ven-

Requests for reprints to Dr Neil P Lewis, Department of Cardiology, University Hospital of Wales, Heath Park, Cardiff CF4 4XN.

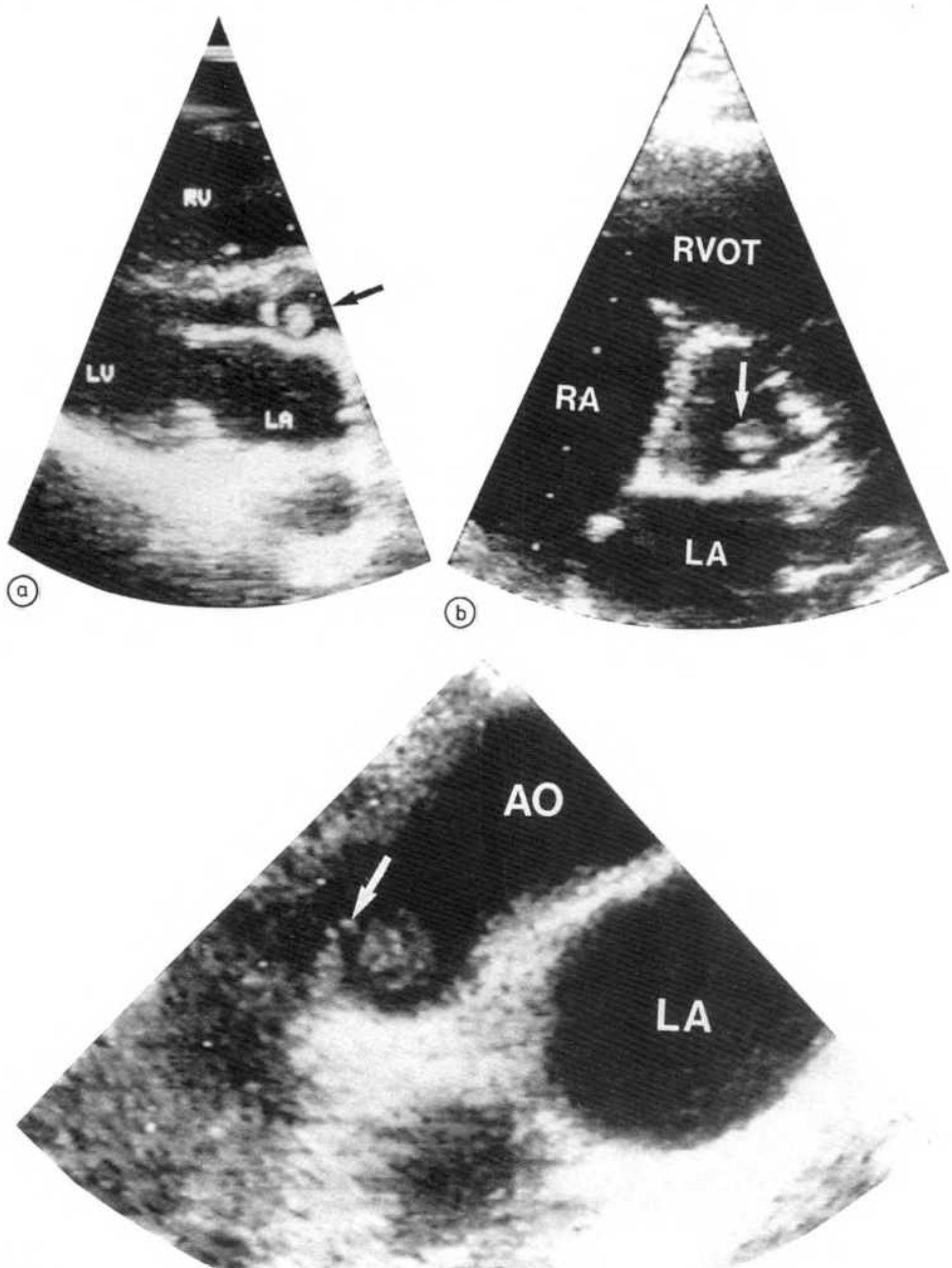


Fig 1 *Cross sectional echocardiographic images showing spherical mass (arrowed) in the aortic root. (a) Parasternal long axis view showing mass in the posterior half of the aortic root. (b) Short axis view showing mass between right and left coronary cusps. LV, left ventricle; LA, left atrium; RV, right ventricle; RVOT, RV outflow tract; RA, right atrium. (c) Intraoperative epicardial echocardiogram showing attachment of the mass by a stalk (arrowed) to the top of the left coronary cusp. AO, ascending aorta; LA, left atrium.*

triculography (performed via the atrial septal defect) nor aortography showed a filling defect in the aortic root.

Early operation was advised because of a possible risk of embolism. At operation, before epicardial bypass, echocardiographic imaging was performed with a 5 MHz probe placed on the aorta. This showed that the mass was attached to the tip of the left coronary cusp of the aortic valve (fig 1c). There was no connection to the free wall of the aorta and the mass remained clearly visible during both systole and diastole. After routine closure of the atrial septal defect with a Dacron patch, the aortic valve was examined through a transverse aortotomy. The mass was attached to the free margin of the left coronary cusp by a stalk, and it consisted of a central papillary core of pale tissue covered by abundant gelatinous material (fig 2a). Grossly it resembled a small cardiac myxoma. The right and non-coronary cusps of the aortic valve appeared normal and the ostia of the coronary arteries were not obstructed. The tumour was removed with a small sliver of the free margin of the left coronary cusp. The competence of the aortic valve after resection was confirmed by fluid instillation into the aortic root, rather than by Doppler colour flow mapping, which was not then available.

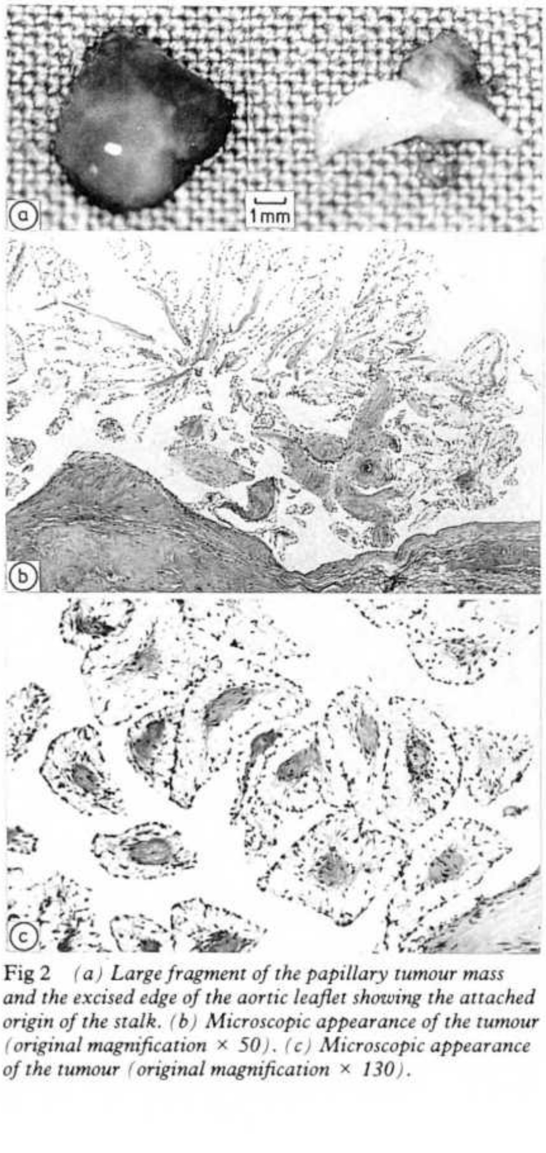


Fig 2 *(a) Large fragment of the papillary tumour mass and the excised edge of the aortic leaflet showing the attached origin of the stalk. (b) Microscopic appearance of the tumour (original magnification × 50). (c) Microscopic appearance of the tumour (original magnification × 130).*

Histopathological examination showed the typical appearance of a so-called papillary tumour of cardiac valves,[6] composed of numerous delicate slender papillae anchored to the aortic valve cusp by a narrow pedicle of fibroelastic tissue. Each papilla consisted of a central acellular eosinophilic core made up of collagen and whorls of elastic fibres, surrounded by a sheath of myxoid material rich in acid mucopolysaccharides and covered by a single layer of flattened, regular endothelial cells (fig 2b,c). There was no evidence of recent thrombosis or of fibrin deposition on the surface of the lesion.

The patient made an uncomplicated recovery. Postoperative echocardiographic examination before discharge showed no residual tumour. There was evidence of mild aortic regurgitation on the continuous wave Doppler echocardiogram, although there was no audible early diastolic murmur.

Discussion

Papillary tumours of the aortic valve typically are attached to the ventricular surface of a cusp,[6] as in the patient of Shub *et al.*[4] The location of the tumour described in the present report, on the free margin and aortic surface, is therefore unusual. There have been reports of similar lesions arising from the leaflets,[2 7 8] papillary muscles,[9] or chordae tendineae[4] of the mitral valve; from the tricuspid valve[10]; or from the endocardium of the septum or outflow tract of the left ventricle.[11-13]

As in other cases, echocardiography in our patient showed a solitary small nodule. Although a diagnosis of infective endocarditis could not be excluded on preoperative imaging from the chest wall, in retrospect the presence of a mass without significant haemodynamic effects or any systemic upset or embolism, made infection unlikely. The precise attachment of the tumour could not be determined from a parasternal approach—as in a previous case in which echocardiography suggested that a papillary tumour was attached to the anterior mitral leaflet when it was in fact attached only to the chordae tendineae[4]—and therefore intraoperative epicardial imaging was very helpful. The clarity of epicardial echocardiographic images may be of particular value where transthoracic images are of poor quality. In our case, epicardial echocardiography showed the stalk of the tumour and excluded other lesions such as aortic root abscess associated with infective endocarditis. It also assisted the surgeon in planning the careful excision of the tumour. In one previous case, transoesophageal echocardiography was used during cardiac operation to examine a papillary tumour arising from the anterior leaflet of the mitral valve.[8] Although no new features were identified on that occasion, intraoperative echocardiography should facilitate more precise diagnosis of a papillary tumour and when allied to colour flow mapping will provide rapid assessment of valve function after excision and valve repair. The images obtained from epicardial and transoesophageal echocardiography are of similar quality, so that the ideal intraoperative technique will depend in part on the anatomical location of each tumour. Epicardial imaging in a sterile operative field can be easily achieved by enclosing the imaging probe in a sterile plastic bag. The ease and convenience of this approach may lead to epicardial imaging becoming the more popular form of intraoperative echocardiography particularly if, as is already practised in some centres, surgeons become familiar with the use of echocardiographic equipment themselves.[14]

In seven out of 12 (including our patient) echocardiographic reports of papillary tumours M mode traces have been normal. Nevertheless, additional echoes have sometimes been seen on the aortic valve,[5] on the anterior mitral leaflet,[4] in the left ventricular outflow tract,[13] or on the tricuspid valve.[10]

The aetiology of papillary tumours is unclear, and this is reflected by the variety of names (at least 16) by which they are known.[7,8,13] In some journals current usage favours the term "fibroelastoma", but until the cause and nature of these lesions are established, we prefer to continue to use the simplest descriptive term, namely papillary tumour.[6] Most cases reported by pathologists occurred in the elderly or in patients with chronic valvitis,[1,6] but in recent years there have been several reports of papillary tumours in patients with a history of previous cardiac operation.[9,10,14] In another patient, several papillary tumours were detected within the left ventricle, eight years after a septal myectomy had been performed.[5] Such cases seem to support the observation that the histological features of papillary tumours are not those of true neoplasms but resemble so-called giant Lambl's excrescences—lesions tht are thought to arise by the organisation of small deposits of fibrin at the sites of minor endothelial damage.[6] It is hard to understand, however, how such a process could give rise to a mass almost 1 cm in diameter, as in our patient, without that mass becoming detached. Some have suggested that both papillary tumours and cardiac myxomas originate from organising mural thrombus,[6,15] because papillary tumours have abundant extracellular acid mucopolysaccharides and a gelatinous consistency similar to that of cardiac myxomas, but this view is at odds with more recent reports of chromosomal abnormalities,[16] abnormal cell differentiation,[17] and neuroendocrine components[18] in myxomas.

Whatever their aetiology, large papillary tumours should probably be removed, even when they are found incidentally during investigations for an unrelated illness, as in our patient. Papillary tumours of the aortic valve in particular have been reported to cause angina[19,20] or death,[20-23] presumably from occlusion of a coronary ostium. Tumours in the left ventricle and on the mitral valve have been associated with recurrent systemic emboli and neurological problems,[7,8,12] and myocardial infarction in a patient with angiographically normal coronary arteries.[7] Systemic embolisation was rarely reported before 1971 (it occurred in three of 39 cases reviewed by Fowles *et al*[7]), but it is more likely that papillary tumours are now being discovered increasingly by echocardiography than that they are being incriminated erroneously as a source of emboli. In two patients thrombus was found on the surface of the tumour on histological examination,[2,7] so anticoagulation should be considered pending surgery. At operation it is usually possible to perform a simple excision of the tumour with conservation,[10] as in our patient, or repair[2,8] of the related valve. There have been no reports of recurrence of a papillary tumour, but echocardiographic surveillance is advisable.

We thank Mr E G Butchart, FRCS, for his help with this patient.

References

1 Abu Nassar SG, Parker JC. Incidental papillary endocardial tumor. Its potential significance. *Arch Pathol* 1971;**92**:370–6.

2 McFadden PM, Lacy JR. Intracardiac papillary fibrolastoma: an occult cause of embolic neurological deficit. *Ann Thorac Surg* 1987;**43**:667–9.

3 Lichtenstein HL, Lee JCK, Stewart S. Papillary tumor of the heart: incidental finding at surgery. *Hum Pathol* 1979;**10**:473–5.

4 Shub C, Tajik AJ, Seward JB, *et al.* Cardiac papillary fibroelastomas. Two-dimensional echocardiographic recognition. *Mayo Clin Proc* 1981;**56**:629–33.

5 Levinsky L, Srinivasan V, Gingell RL, *et al.* Papillary fibroelastoma of aortic and mitral valves following

myectomy for idiopathic hypertrophic subaortic stenosis. *Thorac Cardiovasc Surg* 1981;**29**:187–91.

6 Pomerance A. Papillary "tumours" of the heart valves. *J Pathol Bacteriol* 1981;**81**:135–40.

7 Fowles RE, Miller DC, Egbert BM, Fitzgerald JW, Popp RL. Systemic embolization from a mitral valve papillary endocardial fibroma detected by two-dimensional echocardiography. *Am Heart J* 1981; **102**:128–30.

8 Topol EJ, Biern RO, Reitz BA. Cardiac papillary fibroelastoma and stroke. Echocardiographic diagnosis and guide to excision. *Am J Med* 1986;**80**: 129–32.

9 Cha SD, Incarvito J, Fernandez J, Chang KS, Maranhao VM, Gooch AS. Giant Lambl's excrescences of papillary muscle and aortic valve: echocardiographic, angiographic and pathologic findings. *Clin Cardiol* 1981;**4**:51–4.

10 Frumin H, O'Donnell L, Kerin NZ, Levine F, Nathan LE, Klein SP. Two-dimensional echocardiographic detection and diagnostic features of tricuspid papillary fibroelastoma. *J Am Coll Cardiol* 1983;**2**:1016–8.

11 Flotte T, Pinar H, Feiner H. Papillary elastofibroma of the left ventricular septum. *Am J Surg Pathol* 1980; **4**:585–8.

12 Ong LS, Nanda NC, Barold SS. Two-dimensional echocardiography detection and diagnostic features of left ventricular papillary fibroelastoma. *Am Heart J* 1986;**103**:917–8.

13 Almagro UA, Perry LS,Choi H, Pintar K. Papillary fibroelastoma of the heart. Report of six cases. *Arch Pathol Lab Med* 1982;**106**:318–21.

14 Fraser AG, van Herwerden L, van Daele MERM, Bos E, Roelandt JRTC, Sutherland GR. The relative values of intraoperative epicardial and transoesophageal echocardiography in mitral valve repair [Abstract]. *Br Heart J* 1989;**61**:451.

15 Heath D, Thompson I McK. Papillary "tumours" of the left ventricle. *Br Heart J* 1965;**29**:950–4.

16 Salyer WR, Page DL, Hutchins GM. The development of cardiac myxomas and papillary endocardial lesions from mural thrombus. *Am Heart J* 1975;**89**:4–17.

17 Dewald GW, Dahl RJ, Spurbeck JL, Carney JA, Gordon H. Chromosomally abnormal clones and nonrandom telomeric translocations in cardiac myxomas. *Mayo Clin Proc* 1987;**62**:558–67.

18 Goldman BI, Frydman C, Harpaz N, Ryan SF, Loiterman D. Glandular cardiac myxomas. Histologic, immunohistochemical, and ultrastructural evidence of epithelial differentiation.*Cancer* 1987;**59**:1767–75.

19 Davies MJ, Rode J, Woolf N, Krikler DM. Neuroendocine differentiation in atrial myxomas. *Lancet* 1987;ii:800.

20 Heath D, Best PV, Davis BT. Papilliferous tumours of the heart valves. *Br Heart J* 1961;**23**:20–4.

21 Rona G, Feeney N, Kahn DS. Fibroelastic hamartoma of the aortic valve producing ischemic heart disease. Associated pulmonary globus bodies. *Am J Cardiol* 1983;**12**:869–74.

22 Harris LS, Adelson L. Fatal coronary embolism from a myxomatous polyp of the aortic valve. *Am J Clin Pathol* 1965;**43**:61–4.

23 Butterworth JS, Poindexter CA. Papilloma of cusp of the aortic valve. Report of a patient with sudden death. *Circulation* 1973;**48**:213–5.

Br Heart J 1989;62:475–6

Severe haemolytic anaemia after replacement of the mitral valve by a St Jude medical prosthesis

HARRY FELD, JAMES ROTH

From the Montefiore Medical Center, Albert Einstein College of Medicine, Division of Cardiology, Bronx, New York, USA

SUMMARY Severe haemolytic anaemia developed in a 33 year old patient after the mitral valve was replaced with a St Jude medical prosthesis. This was the patient's third thoracotomy. She had already had a mitral commissurotomy and a mitral valve bioprosthesis. The patient had an E+ antibody to red blood cells as well as a paraprosthetic leak. The haemolysis became less severe once the population of E+ red cells was completely haemolysed. However, the patient continued to require transfusions to remain out of heart failure. Once the valve was replaced, the haemolysis subsided.

Fulminant haemolysis after mitral valve replacement is rare. When it does occur, a paraprosthetic leak should be suspected. Other causes of haemolysis, however, must also be considered and these may contribute to the severity of haemolysis.

Intravascular haemolysis after the placement of a mechanical prosthetic valve is well recognised and occurs in most patients.[1–4] But increased erythropoiesis makes this common form of haemolysis not clinically significant. Fulminant haemolysis after valve replacement is rare and is usually the result of a paraprosthetic leak. We report a case of severe haemolysis after placement of a St Jude valve which was caused by a combination of red blood cell antibodies and a paraprosthetic leak.

Case report

CLINICAL HISTORY AND FINDINGS

A 33 year old black woman presented with haematuria and anaemia several days after placement of a St Jude valve in the mitral position. The patient had a history of rheumatic heart disease as a child and had mitral valve commissurotomy at age 19. When she was 24 the mitral valve was replaced with a bovine bioprosthesis. The patient did well for nine years, then she presented with shortness of breath. Cardiac catheterisation showed an 8 mm end diastolic gradient. Mitral stenosis was diagnosed, and the patient underwent mitral valve replacement with a St Jude valve. Several days after the operation the patient noted the onset of haematuria. Over the next month she was admitted twice with congestive heart failure and anaemia. The patient was admitted to another hospital where she required 18 units of blood over a two week period.

PHYSICAL EXAMINATION

Upon transfer to our hospital, the patient was grossly icteric. The pulse was 90 beats/min, blood pressure 110/70 mm Hg, and temperature 100·8°F. Neck vein distension was present with normal contour. The chest was clear. The heart was hyperdynamic. There was a harsh 3/6 systolic murmur and 1/4 blowing diastolic murmur at the left upper sternal border. At the apex there was a blowing pansystolic murmur. There was no organomegaly or pedal oedema.

LABORATORY DATA

The urine was bloody. Microscopy did not show any red blood cells. The dipstick was 4+ positive for haem. Urine haemosiderin was also present.

The haematocrit was 25% and a smear of peripheral blood showed schistocytes. The total serum bilirubin concentration was 42·8 μmol/l, direct bilirubin was 6·8 μmol/l, and the serum concentration of lactate dehydrogenase was 57·2 μkat/l. Serum haptoglobin was absent. The direct and indirect Coombs tests were negative. The manual polybrene test[5] showed two red blood cell antibodies, E+ antibodies and BGA (or HLA-7) antibodies. These were believed to be secondary to previous transfusions. Analysis of the patient's red blood cells showed that 50% of her red blood cells were E+. The second antibody was not thought to be clinically significant or to contribute to the haemolysis.

Requests for reprints to Dr Harry Feld, Maimonides Medical Center, Division of Cardiology, 4802 Tenth Avenue, Brooklyn, NY 11219, USA

NON-INVASIVE STUDIES

The electrocardiogram was consistent with left atrial enlargement. The chest *x* ray showed a large left atrium and pulmonary vascular redistribution. An echocardiogram showed a moderately enlarged left atrium of 5·2 cm. Left ventricular size and function were normal. The aortic valve was calcified, but opened well. The mitral tilting disc prosthesis seemed grossly normal. Careful Doppler examination did not show any mitral regurgitation.

CARDIAC CATHETERISATION

The right heart catheterisation showed a right atrial pressure of 12 mm Hg, a right ventricular pressure of 75/14 mm Hg and a pulmonary artery pressure of 75/40 mm Hg. The pulmonary capillary wedge pressure wave had an "a" wave of 25 mm Hg and a regurgitant wave of 50 mm Hg. The left ventricular end diastolic pressure was 25 mm Hg. The cardiac output was 4·95 l/min by thermodilution. The left ventriculogram showed severe mitral regurgitation through an infero-posterior paraprosthetic leak. Aortography showed trace aortic insufficiency. The coronary arteries were normal.

Discussion

This patient showed several difficulties encountered in the management of severe haemolytic anaemia after placement of a mechanical valve. Although valve dysfunction is the most likely cause of haemolysis in this type of patient, other causes may contribute and require treatment. The diagnosis of haemolysis was made in the routine fashion. A fall in haematocrit was accompanied by an increased serum concentration of lactate dehydrogenase and indirect bilirubin. Serum haptoglobin was absent. The urine appeared grossly bloody, but microscopical examination did not show any red blood cells. There was haemosiderin in the urine. Microscopical examination of the red blood cells showed schistocytes, which usually suggest mechanical trauma of red blood cells. In this case, however, the presence of schistocytes did not help determine the aetiology of the haemolysis because schistocytes are routinely found in patients with mechanical prosthetic valves. Direct and indirect Coombs tests were negative which made the diagnosis of immunohaemolytic anaemia less likely.

The Coombs test, however, can miss certain antibodies. A manual polybrene test[5] was therefore performed which showed anti-E+ antibodies. Analysis of the patient's red blood cells showed that 50% of her red blood cells were E+. This indicated that a significant component of the haemolysis was caused by red blood cell antibodies. Therefore, in this patient, the only way to differentiate whether the aetiology of the severe haemolysis was due to red blood cell antibodies or mechanical trauma was to follow the patient until the E+ red blood cells which had been transfused into this patient were lysed.

In fact the severe haemolysis in this patient was the result of the combination of red blood cell antibodies and the mechanical trauma of a paraprosthetic leak. We followed the patient for four weeks and limited transfusions to when the patient's haematocrit fell below 25% and symptoms of heart failure developed. The haemolysis became less severe as the E+ red blood cells were eliminated. In the first week she needed nine units of whole blood; in the fourth week she required only two units.

Because important haemolysis persisted despite the absence of E+ red blood cells, a cardiac catheterisation was performed which showed the paravalvar leak. Then we decided to replace the valve despite the high risk of a fourth thoracotomy. The haemolysis resolved immediately when the valve was replaced and there was no haematuria after operation. Follow up confirmed that haemolysis had resolved, and the patient was discharged one week later with a stable haematocrit.

This case confirms that the most likely cause of severe haemolysis after valve replacement is an important paraprosthetic leak. Other causes of haemolysis can contribute to the severity of the haemolysis. In our case, post-transfusion antibodies were detected by the polybrene technique. One of these antibodies contributed significantly to this patient's severe haemolysis.

References

1 Kloster F. Diagnosis and management of complications of prosthetic heart valves. *Am J Cardiol* 1975;35:872–85.

2 Ahmad R, Manohitharajah M, Deverell P, Watson D. Chronic hemolysis following mitral valve replacement. *J Thorac Cardiovasc Surg* 1976;71:212–7.

3 Crexells C, Aerichide N, Bonny Y, Lepage G, Campeau L. Factors influencing hemolysis in valve prosthesis. *Am Heart J* 1972;84:161–70.

4 Rodgers B, Sabiston D. Hemolytic anemia following prosthetic valve replacement. *Circulation* 1969; 39–40(suppl I):I-155–61.

5 Lalezari P, Jiang A. The manual polybrene test: a simple and rapid procedure for detection of red cell antibodies. *Transfusion* 1980;20:206–11.

Br Heart J 1989;**62**:477–81

Hypoplastic right retro-oesophageal aortic arch: similarities to interrupted aortic arch

W B KNIGHT

From the Department of Cardiology, Adelaide Children's Hospital, North Adelaide, South Australia

SUMMARY At echocardiography a dysmorphic neonate was found to have a hypoplastic mitral valve, left ventricle, and ascending aorta with interruption of the aortic arch between the left common carotid and the left subclavian arteries—the left subclavian artery arose from a normal sized left descending aorta. Cardiac catheterisation and subsequent necropsy confirmed this arrangement but also showed a tortuous right retro-oesophageal aortic arch. This arch was severely hypoplastic distal to the right subclavian artery. These cardiovascular anomalies occurred in the child of a family in which other members showed the velo-cardio-facial syndrome, a condition known to be associated with right aortic arch. This aortic arch arrangement may be impossible to distinguish from simple aortic interruption by echocardiography alone.

Cross sectional echocardiography lends itself to the detection of interruption of the aortic arch but the following is an unusual case of a rare arch anomaly with similar clinical findings that can be indistinguishable from simple aortic interruption by echocardiography alone.

Case report

Dysmorphic features were noted soon after birth in a full term 2·8 kg male infant: prominent nose, short mouth, micrognathia, anomalous ears, widely spaced nipples, arachnodactyly, and minor syndactyly of the second and third toes. A large, tense congenital phimosis required surgical incision. There was no erectile tissue palpable in the penis and the glans was not identifiable. He was in mild heart failure with no evidence of cyanosis of upper or lower body. The only palpable peripheral pulse was the right brachial and this was weak. Systolic blood pressures were 70 mm Hg in the right arm, 67 mm Hg in the left arm, and 85 mm Hg in the legs. There was a prominent parasternal impulse. The second heart sound was narrowly split with an accentuated pulmonary component. There was an ejection click and a soft basal ejection systolic murmur. There was no stridor. The electrocardiogram showed right ventricular hypertrophy and the chest radiograph showed mild cardiomegaly and pulmonary congestion. The thymus obscured details of the aortic arch and there was no obvious tracheal deviation.

Cross sectional echocardiography showed normal atrioventricular and ventriculoarterial connections. The right heart chambers were enlarged. The left atrium, mitral valve, and left ventricle were hypoplastic. The end diastolic left ventricular dimension was only 10 mm. A perimembranous ventricular septal defect of moderate size was seen. The pulmonary artery was much larger than the ascending aorta, which had a diameter of only 6 mm. The aortic valve was small but otherwise normal. The ascending aorta did not arch posteriorly but simply bifurcated. The descending aorta was to the left of the spine and of normal size. It was connected to the pulmonary artery by way of the ductus arteriosus, which was only slightly constricted. The left subclavian artery arose from its postero-superior extremity.

Cardiac catheterisation showed a large left to right atrial and ventricular shunt with equal systolic pressures in both ventricles and pulmonary trunk. There was a 20 mm Hg systolic pressure drop across the ductus arteriosus to the descending aorta. The ascending aorta was not entered. Cineangiography confirmed the echocardiographic details of cardiac anatomy. Separate injections of contrast into the left ventricle (fig 1a and b) and ductus arteriosus (fig 1c) confirmed a lack of continuity between the left common carotid and left subclavian arteries. However, the right branch of the bifurcation of the ascending aorta was not an innominate artery—as

Requests for reprints to Dr W B Knight, Department of Cardiology, Adelaide Children's Hospital, 72 King William Road, North Adelaide, South Australia 5006, Australia.

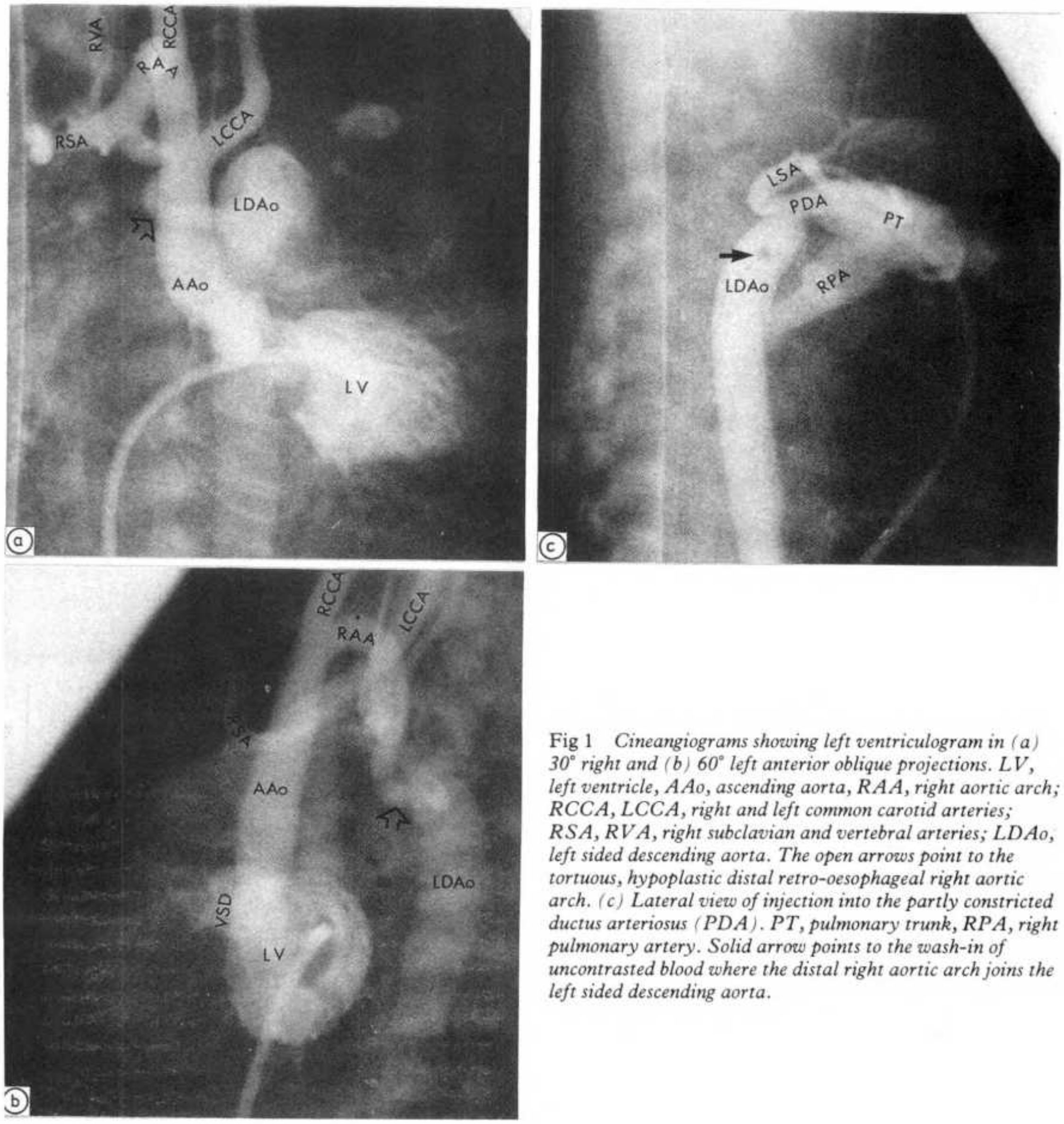


Fig 1 *Cineangiograms showing left ventriculogram in (a) 30° right and (b) 60° left anterior oblique projections. LV, left ventricle, AAo, ascending aorta, RAA, right aortic arch; RCCA, LCCA, right and left common carotid arteries; RSA, RVA, right subclavian and vertebral arteries; LDAo, left sided descending aorta. The open arrows point to the tortuous, hypoplastic distal retro-oesophageal right aortic arch. (c) Lateral view of injection into the partly constricted ductus arteriosus (PDA). PT, pulmonary trunk, RPA, right pulmonary artery. Solid arrow points to the wash-in of uncontrasted blood where the distal right aortic arch joins the left sided descending aorta.*

had been assumed from echocardiography. It gave rise to the right common carotid artery and then arched posteriorly to the right of the trachea to give rise to the right subclavian artery. Beyond this point it became narrow (minimal internal diameter 2 mm) and tortuous and crossed the midline behind the oesophagus to join the left descending aorta just distal to the origin of the latter from the partly constricted arterial duct (fig 1c). It was thus a retro-oesophageal right aortic arch, severely hypoplastic and tortuous in its distal portion, associated with an anomalous origin of the left subclavian artery.

Serum calcium, T cell function, and numbers and chromosome analysis were normal. He died when he was nine days old. Necropsy confirmed the cardiovascular abnormalities including small tortuous right aortic arch (figs 2a and b). The ventricular septal defect accepted a probe of 6 mm. The ascending aorta was only 4 mm in diameter. The aortic valve was small but not stenotic. A persistent left superior

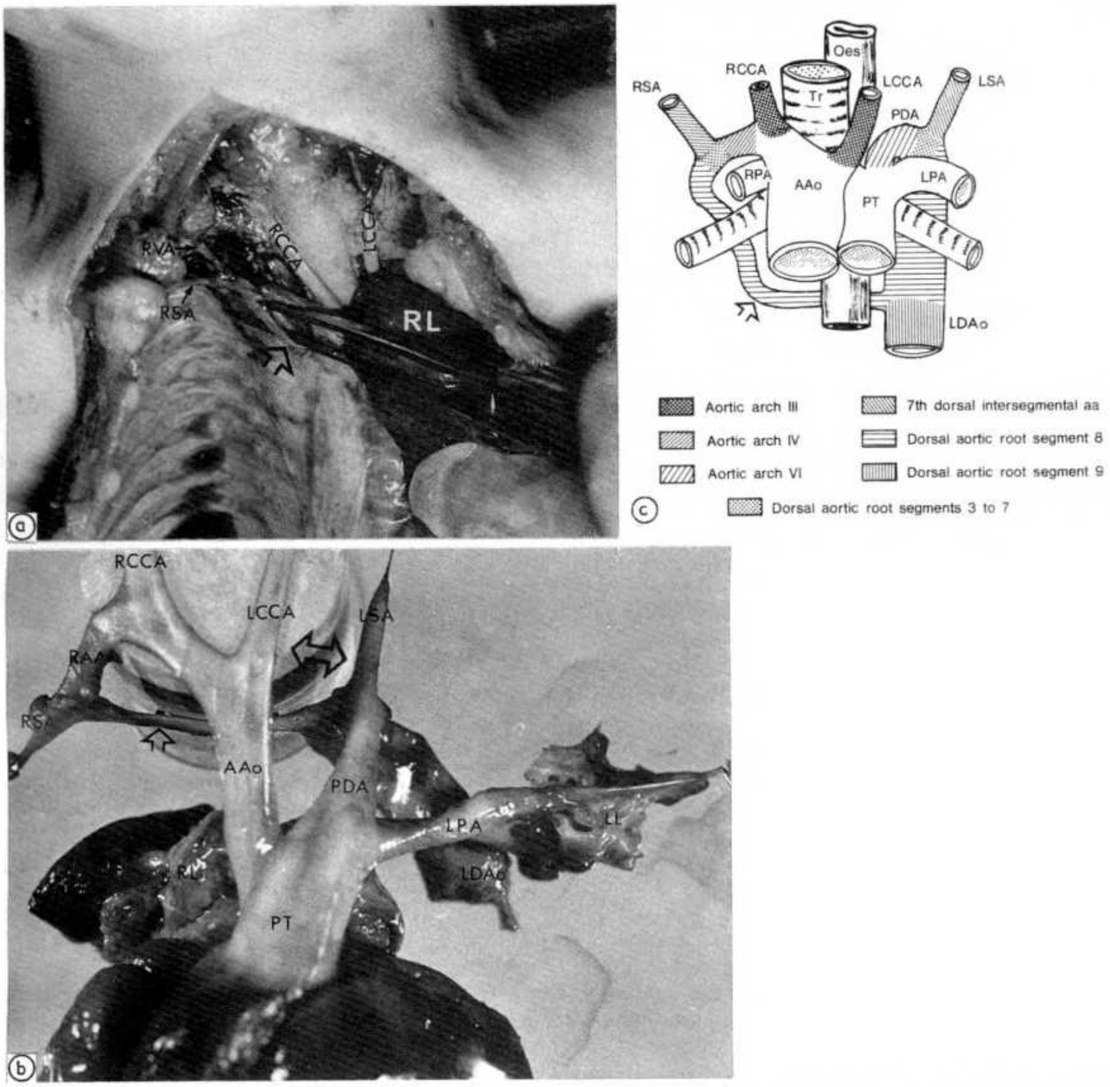


Fig 2 *(a) Anatomical specimen showing right aortic arch looped around forceps, passing behind the oesophagus and (b) the dissected heart and great arteries as seen from the front. The double headed arrow shows the "interruption" between the left common carotid artery and left subclavian artery while the open arrow points to the stretched hypoplastic distal right aortic arch. LPA, left pulmonary artery; LL, RL, hilar portions of left and right lungs. See legend to fig 1 for other abbreviations. (c) Diagram of (b) indicating the presumed embryological origin of the vascular structures. Tr, trachea, Oes, oesophagus.*

vena cava drained to the coronary sinus. Only a very small amount of penile erectile tissue was present. The remainder of the renal tract was normal. An unsuspected finding was a bifid uvula.

The father of this patient has a left aortic arch and no known cardiac abnormalities, but he has dysmorphic facial features including narrow palpebral fissures, malar and maxillary hypoplasia, a prominent nose with tented alae nasi, short philtrum, large mouth, and bat ears. He has a repaired cleft palate. He described himself as a slow learner. A subsequent son was born with similar facial dysmorphism and bifid uvula. He has undergone open heart surgery for a large ventricular septal defect. The father and two sons are thought to have the velo-cardio-facial syndrome.

Discussion

A right aortic arch crosses over the right rather than the left bronchus. It has been classified into two types[1]: (*a*) a simple or anterior type in which the transverse arch is anterior to the trachea and oesophagus, as in normal individuals, and the upper descending aorta is to the right side of the spine (the type commonly seen in cases of tetralogy of Fallot or common arterial trunk); (*b*) a posterior or retro-oesophageal type in which the transverse arch passes to the right of and posterior to the trachea and oesophagus and the upper descending aorta lies more to the left than in the anterior type and frequently gives rise to a diverticulum from which arise an anomalous left subclavian artery and the ductus arteriosus or ligament, resulting in a vascular ring.[2] The latter type is said to be uncommonly associated with congenital heart defects[1] and according to Edwards[3] is the second most common cause of compression of the oesophagus after a right subclavian artery arising anomalously from an otherwise normal left sided aorta. Our patient had a posterior retro-oesophageal right aortic arch complicated by a cardiac lesion that was expected to have reduced the fetal blood flow in the ascending aorta and not unexpectedly therefore was associated with severe hypoplasia of the distal right arch.

Echocardiographic findings in this case were typical of those found in type B interruption of the aortic arch[4] in that the usual posterior curvature of the arch was absent and there was an obvious discontinuity between the bifurcating ascending aorta and the (left) descending aorta from which the left subclavian artery arose. The left arterial duct connected the pulmonary artery to the descending aorta. In many centres such clear demonstration of cardiac and great artery anatomy in a sick neonate by cross sectional echocardiography has obviated the need for preoperative cardiac catheterisation and cineangiography. Accurate echocardiographic diagnosis of the abnormality of the aortic arch in our patient was made difficult by the hypoplasia and tortuosity of the distal right arch. In addition, because the echocardiographic appearances were consistent with the clinical signs, the presence of an obstructive right retro-oesophageal aortic arch was neither suspected nor specifically searched for. To my knowledge there have been only two previous descriptions of the echocardiographic appearances of retro-oesophageal right aortic arch[5 6]—both had a right cervical aortic arch.

In a search of published reports I found two cases of retro-oesophageal right aortic arch with an aberrant left subclavian artery and hypoplastic distal right arch, both associated with a large ventricular septal defect.[7 8] Both are described as "double aortic arch" with "interruption" of the left arch, despite a stated lack of continuity between the left common carotid and left subclavian arteries. In so far as normal aortic arch anatomy, with one continuous arch (the left one) and persisting remnants of the contralateral arch (such as the innominate artery, being derived from the right fourth aortic arch), could also be described as double aortic arch with interruption of one of the arches, this description does not seem useful or logical, particularly if double aortic arch is defined by the presence of luminal or fibrous continuity of bilateral aortic arches. In both the reported cases[7 8] there was a good response to pulmonary banding alone, presumably because hypoplasia of the right aortic arch was not critical. Indeed left aortic arch atresia with hypoplastic right retro-oesophageal arch (that is double aortic arch with aortic arch atresia) was reported in a patient who was symptom free for 21 years.[9] However, if hypoplasia of the right arch is severe enough, definitive arch surgery may be required as urgently as for classic aortic interruption. The vascular ring associated with right retro-oesophageal aortic arch and left arterial duct does not usually produce compressive symptoms in infancy, but these may appear later in life.[10] Hence the importance of dividing the ring at the time of definitive aortic operation.

It has been noted that in patients with right retro-oesophageal arch, the arch often extends to a higher level in the thorax than in patients without a retro-oesophageal segment.[1 10] This can be seen in the present patient (fig 2a). In addition, obvious tortuosity is seen on angiography (fig 1a). Some cases of cervical arch, most of which have a right retro-oesophageal segment and anomalous left subclavian artery arising from a diverticulum on the left sided descending aorta, may represent the extreme end of the spectrum of retro-oesophageal right (or left) aortic arch in which there is considerable impairment of the normal contraction of the aortic arch and consequent failure of its migration into the chest.

There seems little doubt that this patient, his brother, and father have the velo-cardio-facial syndrome,[11 12] an inherited condition comprising cleft palate (either overt or submucous), learning disability, facial dysmorphism, and cardiovascular malformations. Although thought to be autosomal dominant, male to male transmission has not been described until recently.[13] The mode of inheritance in this family seems to confirm the autosomal dominant nature of this condition. In a survey of 39 patients with velo-cardio-facial syndrome, cardiovascular anomalies occurred in 84%.[12] The most common malformations were ventricular septal defect and right aortic arch, the latter being of both anterior and posterior types.[14] These were both present in the index case as well as persistent left superior vena cava, another known associated anomaly. A subsequent sibling had a large ventricular septal defect requiring surgical closure at three weeks of age. To my knowledge, hypoplasia of the left heart structures has not been reported to occur in velo-cardio-facial syndrome. Similarly, the penile anomaly is not a recognised feature. Fetal echocardiography may have an important role in the prenatal detection of this syndrome.

References

1 Eisen D. Right aortic arch with report of eight cases. *Radiology* 1944;42:570–8.

2 Gross RE, Ware PF. The surgical significance of aortic arch anomalies. *Surg Gynecol Obstet* 1946;83:435–48.

3 Edwards JE. Retro-oesophageal segment of the aortic arch, right ligamentum arteriosum causing congenital vascular ring about the trachea and esophagus. *Mayo Clin Proc* 1948;23:108–16.

4 Celoria GC, Patton RB. Congenital absence of the aortic arch. *Am Heart J* 1959;58:407–14.

5 D'Cruz IA, Stanley A, Vitullo D, Desai P, Chiemmongkoltip P. Non-invasive diagnosis of right cervical aortic arch. *Chest* 1983;83:820–2.

6 Kveselis DA, Snider AR, Dick M, Rocchini AP. Echocardiographic diagnosis of right aortic arch with a retroesophageal segment and left descending aorta. *Am J Cardiol* 1986;57:1198–9.

7 Brenner JI, Berman MA, Talner NS, Stansel HC. Double aortic arch system producing obstruction to left ventricular outflow. *Am J Cardiol* 1974;34:854–6.

8 Collins-Nakai RL, Parisi-Buckley L, Fyler DC, Castaneda AR. Interrupted aortic arch in infancy. *J Pediatr* 1976;88:959–62.

9 Blackford LM. Coarctation of the aorta. *Arch Intern Med* 1928;41:702–35.

10 Felson B, Palayew MJ. The two types of right aortic arch. *Radiology* 1963;81:745–59.

11 Strong WB. Familial syndrome of right-sided aortic arch, mental deficiency, and facial dysmorphism. *J Pediatr* 1968;73:882–8.

12 Shprintzen RJ, Goldberg RB, Young D, Wolford L. The velo-cardio-facial syndrome: a clinical and genetic analysis. *Pediatrics* 1981;67:167–72.

13 Williams MA, Shprintzen RJ, Goldberg RB. Male-to-male transmission of the velo-cardio-facial syndrome: a case report and review of 60 cases. *J Craniofac Genet Dev Biol* 1985;5:175–80.

14 Young D, Shprintzen RJ, Goldberg RB. Cardiac malformations in the velocardiofacial syndrome. *Am J Cardiol* 1980;46:643–8.

Br Heart J 1989;62:482–7

British cardiology

Staffing in cardiology in the United Kingdom 1988
Fifth biennial survey

DOUGLAS CHAMBERLAIN, LINDA BAILEY, EDGAR SOWTON,
DAVID BALLANTYNE, DENNIS McC BOYLE, MICHAEL OLIVER

From The Sussex Centre for Medical Research, University of Sussex, Brighton, in collaboration with the Cardiology Committee, Royal College of Physicians of London and the British Cardiac Society

SUMMARY This is the fifth survey of staffing (consultants and senior registrars) in cardiology in the United Kingdom. Data from previous years—including the fourth survey (1986) that was not published separately—are used to show the trends over the past decade. In 1988 there were less than six cardiologists per million population. The United Kingdom, with Ireland, has fewer cardiologists than all other European countries with reliable figures. The ratio for Europe as a whole is approximately 45 per million population; the recommended figure for the United States of America is 60 per million. The distribution of cardiologists in England and Wales is still very uneven. Seven million people—nearly 15% of the population—have no immediate access to special expertise in cardiology. Women are particularly poorly represented in the speciality.

This survey indicates that the crisis in staffing for cardiology continues. It will worsen as the possibilities grow for effective management of heart disease and as needs increase with the greater average age of the population. Resolution of this crisis should be a major priority in policies aimed at countering the ravages of heart disease.

Staffing and facilities in cardiology in the United Kingdom have been monitored since 1978. Cardiologists were one of the first speciality groups to do so, with the twin intentions of identifying deficiencies in the provision of services throughout the country and of providing information that would aid matching of training posts to future consultant vacancies.

Three surveys have been published.[1-3] These were all conducted from the Centre for Medical Research within the University of Sussex, on behalf of the British Cardiac Society and the Cardiology Committee of the Royal College of Physicians of London. The fourth survey related to consultants and senior registrars only. It was to have been undertaken by the British Cardiac Society, but changes of staff led to unforeseen delays, and the data—with an index date of 1 July 1986—were not published. They are, however, included with this report that deals primarily with information on staffing with an index date of 1 April 1988 (for senior registrars) and one of 1 July 1988 for consultants.

Methods of inquiry

A cardiologist in each health region of England and Wales was sent a list of district contacts to confirm that these contacts were still in post and likely to complete a questionnaire. We used a different method to survey the Health Boards of Scotland and the Health and Social Service Area Boards of Northern Ireland: two of us (DB and DMcCB) collected these data. In previous surveys it was more difficult to obtain information from Scotland and Northern Ireland because of the different organisation of health care. On this occasion the new method of collecting data for Scotland and Northern Ireland proved more successful. We therefore believe that our current data are substantially accurate; but comparisons for Scotland and Northern Ireland that depend on information from previous surveys were included only when we believed that they were accurate.

Requests for reprints to Dr Douglas Chamberlain, Royal Sussex County Hospital, Brighton, Sussex BN2 5BE

Table 1 *Number of cardiologists (cardiovascular physicians) in England and Wales, 1980–1988*

	1980			*1982*			*1984*			*1986*			*1988*		
	Adult	*Paediatric*	*Total*	*Adult*	*Paediatric*	*Total*	*Adult*	*Paediatric*	*Total*	*Adult*	*Paediatric*	*Total*	*Adult*	*Paediatric*	*Total*
Cardiology only	103	19	122	111	18	129	111	29	140	119	31	150	130	33	163
Major interest	98	3	101	117	4	121	121	6	127	118	2	120	127	0	127
Totals	201	32	223	228	22	250	232	35	267	237	33	270	257	33	290

The main questionnaire had two sections: one for consultant staff who practise only cardiology and the other for general physicians with a major interest in the specialty—that is a special interest in cardiology, appropriate training in the speciality, and at least 40% of professional time devoted to it. As before, we recognise that many other physicians, unable to meet all three criteria, provide important services to those with heart disease; but unless all three criteria were met they were not included in the study.

After the questionnaires were returned, the results were assembled by region or by other appropriate groups and submitted under confidential cover to our regional advisers for scrutiny as a guard against inadvertent errors. We identified discrepancies between these data and our previous inquiries at district level and referred them for confirmation or correction.

We obtained information on senior registrars by a separate questionnaire sent to each major cardiac centre.

In general, we retained the format of relevant tables in our previous publication. New tables were included to summarise the changes over the decade.

Comment

Table 1 shows the total number of cardiologists (or cardiovascular physicians) in England and Wales in five surveys from 1980 to 1988. The numbers have increased overall by 30% over the eight years (average 3·8% per year), but most of the increase has been among those practising exclusively either adult cardiology or paediatric cardiology rather than among physicians with a major interest in cardiology. This is disappointing in view of the deficiencies at district level highlighted in earlier reports.

Table 2 shows the cardiologists in post for all the regions of England and Wales and for the special hospitals. One less health district is included under the special hospitals because of the closure of the country branch of the Brompton Hospital at Frimley. In Wales each district has two general hospitals; the numbers for both these units are shown.

The total number of cardiologists within the regions shows wide disparities that do not appropriately reflect the differences in population. For example the South Western region has one cardiologist for every 246 500, whereas North West

Table 2 *Number of cardiologists (cardiovascular physicians) in England and Wales by region at 1 July 1988*

			Cardiology only		*Major interest*		
Region	*Population**	*No of HDs*	*Adult*	*Paediatric*	*Adult*	*Paediatric*	*Total*
East Anglia	2 103 700	8	3	0	6	0	9
Mersey	2 408 700	10	4	3	5	0	12
Northern	3 076 800	16	6	2	11	0	19
North East Thames	3 771 500	16	12	0	10	0	22
North West Thames	3 488 300	15	16	2	7	0	25
North Western	3 991 100	19	9	2	12	0	23
Oxford	2 501 800	8	4	2	7	0	13
South East Thames	3 635 400	15	15	4	8	0	27
South West Thames	2 959 600	13	6	0	8	0	14
South Western	3 205 500	11	5	2	6	0	13
Trent	4 646 300	12	6	1	11	0	18
Wessex	2 905 600	10	2	2	8	0	12
West Midlands	5 197 700	22	13	3	11	0	27
Yorkshire	3 604 700	17	10	3	9	0	22
Wales	2 836 200	9†	5	0	8	0	13
Special hospitals		4	14	7	0	0	21
Totals‡	50 242 900	205	130 (119)	33 (31)	127 (118)	0 (2)	290 (270)

*Office of Population Censuses and Surveys' estimate for mid 1987.
†The nine Welsh health districts have 18 district hospitals
‡1986 data (previously unpublished) in parentheses
HD, health district.

Table 3 *Number of cardiologists (cardiovascular physicians) in Scotland by health board at 1 July 1988*

		Cardiology only		*Major interest*		
Health board	*Population (1987)*	*Adult*	*Paediatric*	*Adult*	*Paediatric*	*Total*
Argyll and Clyde	443 128	0	0	0	0	0
Ayrshire and Arran	374 752	0	0	0	0	0
Borders	102 141	0	0	0	0	0
Dumfries and Galloway	147 036	0	0	0	0	0
Fife	344 590	0	0	0	0	0
Forth Valley	272 077	0	0	0	0	0
Grampian	502 863	3	0	0	0	3
Greater Glasgow	951 219	11	3	2	0	16
Highland	200 608	0	0	0	0	0
Lanark	563 448	0	0	0	0	0
Lothian	743 700	5	2	0	0	7
Orkney	19 338	0	0	0	0	0
Shetlands	224 290	0	0	0	0	0
Tayside	393 762	2	0	0	0	2
Western Isles	31 048	0	0	0	0	0
Totals	5 314 000	21	5	2	0	28

Thames has one cardiologist for every 140 500.

Tables 3 and 4 show the numbers of cardiologists in Scotland and in Northern Ireland. The concentration of cardiologists within the Eastern Health Board of Northern Ireland is accounted for by the site of the centre for the whole of the province. Since the last report, Belfast has one fewer cardiologist. Four cardiologists meeting our criteria as having a major interest have, however, been appointed in neighbouring district hospitals.

Table 5 shows the number of retirements expected each year for cardiovascular physicians in post in England and Wales. We compared these totals with predictions from earlier years. In general terms there is good agreement, but inevitably some cardiologists do change their plans; the prediction will not always be fulfilled each year. There is a tendency for retirement to be planned for age 60, but for it then to be deferred. Few retirements are expected from 1990 to 1996, except for 1993 when nine replacement posts should become vacant. The numbers of retirements should increase thereafter (the data are shown only to the year 2000). Over the next 15 years a similar number of vacancies are expected in both full time cardiology and in general medicine with major interest in the subject. For the 11 years 1989 to 1999 the figures are 37 and 35 respectively. There will, of course, be unexpected vacancies and new posts will continue to be created.

Tables 6 and 7 show retirement data for Scotland and Northern Ireland. Up to 1998 only 10 vacancies are expected for the two countries combined.

Table 8 shows the number of health districts within each region that still have no physicians employed full time in cardiology or with a major interest in cardiology. The number was 63 in 1982, 57 in 1984, 54 in 1986, and 46 in mid 1988. There are, however, over seven million people in England and Wales (nearly 15 per cent of the population) who have no immediate access to special expertise in cardiology. The situation may, in fact, be somewhat worse than this. In several regions specialists attempt to cover more than one health district. A health district may therefore claim to have a cardiologist on the grounds that one or more sessions per week are covered from, for example, the regional centre. We know that in some regions this arrangement is regarded as satisfactory, but in others it is not.

Table 9 shows 11 Scottish Health Boards without a specialist cardiological physician, and this seems to show a position that has deteriorated since 1984. The change, however, is apparent rather than real and

Table 4 *Number of cardiovascular physicians in Northern Ireland by health board at 1 July 1988*

		Cardiology only		*Major interest*		
Health board	*Population (1986)*	*Adult*	*Paediatric*	*Adult*	*Paediatric*	*Total*
Eastern	642 100	10	2	3	0	15
Northern	379 000	0	0	3	0	3
Southern	288 900	0	0	3	0	3
Western	256 800	0	0	3	0	3
Totals*	1 566 800	10 (11)	2 (2)	12 (8)	0 (0)	24 (21)

*1986 data (previously unpublished) are shown in parentheses.

Table 5 *Number of cardiologists (cardiovascular physicians) retiring each year in England and Wales (as of 1 July 1988)*

	Cardiology only			*Major interest*			
Year	*Adult*	*Paediatric*	*Total*	*Adult*	*Paediatric*	*Total*	*Grand total*
1988	3	1	4	1	0	1	5
1989	4	1	5	2	0	2	7
1990	2	0	2	1	0	1	3
1991	3	0	3	2	0	2	5
1992	2	0	2	2	0	2	4
1993	5	1	6	3	0	3	9
1994	3	0	3	1	0	1	4
1995	4	0	4	1	0	1	5
1996	3	0	3	3	0	3	6
1997	3	0	3	7	0	7	10
1998	2	0	2	4	0	4	6
1999	3	1	4	9	0	9	13
2000+	93	29	122	91	0	91	213
Totals	130	33	163	127	0	127	290

indicates only a change in designation. Only three units of management within Northern Ireland (table 10) are without specialist cardiologists, but the position is regarded as satisfactory in two of these and is difficult to correct in the third because a small population is scattered over a large area.

Table 11 compares the number of senior registrars with the present number of specialist consultant posts for England and Wales. The ratio varies from 14:1 to 4:1. The disparate ratios reflect in part the number and size of the cardiac centres within the regions, and the inequality of distribution is not regarded as especially undesirable. Broadly speaking, the distribution of senior registrars within regions is also satisfactory.

Table 12 compares registrars' contract expiry dates and physicians' retirement dates between 1988 and 1992 for England and Wales. It shows that 30 more senior registrar contracts will expire than physicians will retire. The comparable figure in our last report (for 1984) was 21. The apparent excess during that period did not lead to any increase in the number of senior registrars who became time expired, and indeed fewer became time expired. Several new posts have been filled since the index date of our report, and we do not regard the present situation as unsatisfactory. Indeed, we predict that there will be a reasonable balance over the next few years, and a possible dearth of fully trained senior registrars within seven or eight years.

There are also seven registrars in Scotland training in cardiology and three in Northern Ireland (table 13).

Another imbalance does cause us concern and is

Table 6 *Number of cardiologists (cardiovascular physicians) retiring each year in Scotland (as of 1 July 1988)*

	Cardiology only			*Major interest*			
Year	*Adult*	*Paediatric*	*Total*	*Adult*	*Paediatric*	*Total*	*Grand total*
1989	2	0	2	0	0	0	2
1990	0	1	1	0	0	0	1
1991	1	0	1	0	0	0	1
1993	1	0	1	0	0	0	1
1998	1	0	1	1	0	1	2
2000+	16	4	20	1	0	1	21
Totals	21	5	26	2	0	2	28

Table 7 *Number of cardiologists (cardiovascular physicians) retiring each year in Northern Ireland (as of 1 July 1988)*

	Cardiology only			*Major interest*			
Year	*Adult*	*Paediatric*	*Total*	*Adult*	*Paediatric*	*Total*	*Grand total*
1992	1	0	1	0	0	0	1
1997	1	0	1	0	0	0	1
1998	1	0	1	0	0	0	1
2000+	7	2	9	12	0	12	21
Totals	10	2	12	12	0	12	24

Table 8 *Regions and number of health districts without cardiovascular physicians at 1 July 1988 (England and Wales)*

Region	*No of HDs*	*HDs without*	*Regional pop**	*Pop without**
East Anglia	8	1 (−3)	2 013 700	187 900
Mersey	10	6	2 408 700	1 151 400
Northern	16	6	3 076 800	994 200
North East Thames	16	0	3 771 500	0
North West Thames	15	2 (−1)	3 488 300	526 000
North Western	19	5 (−1)	3 991 100	863 700
Oxford	8	0	2 501 800	0
South East Thames	15	1	3 635 400	220 600
South West Thames	13	1 (−2)	2 959 600	276 300
South Western	11	2 (−1)	3 205 500	344 000
Trent	12	3 (−2)	4 646 300	884 300
Wessex	10	3	2 905 600	696 100
West Midlands	22	4 (+2)	5 197 700	748 700
Yorkshire	17	3	3 604 700	469 800
Wales	9/18†	8 (−1)	2 836 200	
Special hospitals	4	0	—	—
Totals	205/214	45 (54)	50 242 900	7 363 000

*Office of Population Censuses and Surveys' estimate for mid 1987.
†The nine Welsh health districts have 18 district hospitals (eight of which are without cardiovascular physicians)
Changes from 1989 are given in parentheses
HDs, health districts

worthy of comment. Women are poorly represented in specialist cardiology. We do not accept the explanation that the training is onerous and that women may not be in a position consistently to meet the demands that are made. If this were true then the workload would be inappropriate for any trainee. Rather we believe that bias—conscious or otherwise—enters into selection. At present only four of the 130 individuals practising adult cardiology full time are women. Many excellent applicants have had unexpected difficulties in progressing to senior registrar posts and excellent female senior registrars have had undue difficulty in becoming consultants. We hope that changes in attitude will correct the serious imbalance.

We believe that the United Kingdom has far too few posts for consultant cardiologists, both in the major centres and in district hospitals. The need has increased substantially in recent decades. Technological, pharmaceutical, and surgical advances offer new opportunities for successful treatment that all too often cannot be made available to patients. This is often because of a shortage of staff rather than

Table 9 *Scottish health boards without cardiovascular physicians at 1 July 1988*

Health board	*Pop without (mid 1987 estimate)*
Argyll and Clyde	443 118
Ayrshire and Arran	374 752
Borders	102 141
Dumfries and Galloway	147 036
Fife	344 590
Forth Valley	272 077
Highland	200 608
Lanark	563 448
Orkney	19 338
Shetlands	22 429
Western Isles	31 048
Total for the 11 boards	2 520 585

Table 10 *Northern Ireland health boards and number of units of management (UOM) without cardiovascular physicians at 1 July 1988*

Health board	*No of UOMs*	*UOMs without*	*Health board pop (1986)*	*Pop without (1986)*
Western	3	0	256 800	0
Eastern	6	2	642 100	175 200
Northern	4	1	379 000	129 800
Southern	3	0	288 900	0
Totals	16	3	1 566 800	305 000

Table 11 *Number of cardiovascular and senior registrars by region of England and Wales at 1 July 1988*

Region	*No of HDs*	*Cardiology only*	*Major interest*	*Senior registrars*
East Anglia	8	3	6	1
Mersey	10	7	5	3
Northern	16	8	11	3
North East Thames	16	12	10	4
North West Thames	15	18	7	4
North Western	19	11	12	4
Oxford	8	6	7	3
South East Thames	15	19	8	4
South West Thames	13	6	8	1
South Western	11	7	6	2
Trent	12	7	11	4
Wessex	10	4	8	2
West Midlands	22	16	11	4
Yorkshire	17	13	9	5
Wales	9/18*	5	8	3
Special hospitals	4	21	0	9
Totals	205/214	163 (150)	127 (120)	56

*The nine Welsh health districts have 18 district hospitals.
Totals for 1986 are given in parentheses.

Table 12 *Senior registrars' contract expiry compared with cardiovascular physicians retirement years for England and Wales only*

Year contract expires	*Contracts expiring*	*Physicians retiring*	*Balance*
1988	10	5	−5
1989	7	7	0
1990	15	3	−12
1991	11	5	−6
1992	11	4	−7
No expiry date*	2	0	2
Totals	56	24	−30

*There are two physicians with permanent contracts in posts designated as having senior registrar status.

There are 30 senior registrars whose contracts expiry dates are not known. These have been assumed to end their contracts four years after appointment or in 1988, if appointed before 1984.

Table 13 *Expiry dates of senior registrars' contracts in Scotland and Northern Ireland*

Year	*Scotland*	*Northern Ireland*
1989	2	0
1990	3	0
1991	1	1
1992	1	2
Total	7	3

for reasons of cost constraint. Prevention, education at all levels, rehabilitation, and community care are needs poorly met by cardiologists who are forced by circumstances to restrict their time to the more technological aspects of their work. Most of the western world is much better served. Direct comparison of numbers of cardiologists in posts in different countries is difficult because there is no universally agreed definition of a cardiologist. But even a superficial consideration of numbers can make the point. The number per million for the United Kingdom of those practising the specialty full time (adult or paediatric) is 3·6. If all physicians with a major interest as defined in this survey are included, the number per million is still less than six. Table 14 shows data collected by the European Society of Cardiology on the number of "currently qualified cardiologists" in other countries (where numbers are known). The ratio for Europe as a whole is approximately 45 per million population. The recommendation by the American College of Cardiology for the number of board certified cardiologists in the United States was 60 per million as long ago as 1974.[4]

Table 14 *Data collected by the European Society of Cardiology* on the number of currently qualified cardiologists in other countries*

Country	*No/ million*	*Country*	*No/ million*
Belgium	27	Sweden	46
Federal Republic of Germany	13	Turkey	8
German Democratic Republic	26	Netherlands	30
Greece	90	Ireland	4
Portugal	42	Italy	118
Austria	20	France	65
Czechoslovakia	20	Switzerland	40
Finland	10	Yugoslavia	30
Hungary	37	Denmark	16
Norway	37	Spain	55

*From report on monospecialty section on Cardiology of the UEMS on training requirements and facilities in Europe in 1989. (MFO).

It may not be realistic to expect that the whole community in the United Kingdom can receive a reasonably comprehensive service for basic cardiological requirements within the next few years, but it is unacceptable that nearly 15% of the population have no immediate access to special expertise in cardiology. Many have no provision even for temporary pacing, and even where this emergency procedure was available in district hospitals the complication rate was unduly high[5] (and N A Boon, personal communication). We believe that the problems highlighted by pacing apply equally to other procedures, which can affect the well-being of patients with heart disease.

Thus the staffing crisis continues and it will worsen as the population ages. While efforts to prevent heart disease, particularly coronary disease, must proceed, resolution of this crisis should be a major priority for those who are responsible for providing adequate staffing.

References

1 Chamberlain DA, Goodwin JF, Emanuel RW, Bailey LG. Career prospects in cardiology in England and Wales. Survey of 15 health regions. *Br Heart J* 1981;45:460–3.

2 Chamberlain D, Bailey L, Emanuel R, Oliver M. Staffing and facilities in cardiology in England and Wales July 1982. Second biennial survey. *Br Heart J* 1983;50:597–604.

3 Chamberlain D, Bailey L, Julian D. Staffing and facilities in cardiology in the United Kingdom 1984. Third biennial survey. *Br Heart J* 1986;55:311–20.

4 Adams FH, Mendenhall RC. Evaluation of cardiology training and manpower requirements. DHEW publication 1974;No. (NIH) 74–623. (Quoted in American College of Cardiology and Health Resources Administration DHEW. Cardiology manpower (9th Bethesda Conference.) *Am J Cardiol* 1976; 37:941–83.

5 Winner SJ, Boon NA. Hazards associated with the use of temporary pacemakers before permanent pacing [Abstract]. *Br Heart J* 1989;61:96

Br Heart J 1989;62:488

Book review

Workshop on coronary heart disease

Trends in Coronary Heart Disease Mortality. The influence of medical care. Edited by Millicent W Higgins and Russell V Luepker. (pp 302: £32.00.) Oxford: Oxford University Press, 1988. ISBN 0-19-505297-8.

The Committee of Public Accounts, in their report on coronary heart disease, have accorded a verdict of "deplorable" to Britain's attempts to reduce mortality from coronary heart disease over the past two decades.[1] The King's Fund consensus statement, after their forum on "Blood cholesterol measurement in the prevention of coronary heart disease", recommends a national food and health strategy to reduce the general concentration of blood cholesterol in the population.[2] Britain has suddenly become publicly conscious that it leads the world league table for deaths from coronary heart disease. It is only because Britain is so far behind the United States in confronting the issues relating to coronary heart disease, that this publication—based on a workshop convened by the National Heart, Lung and Blood Institute in December 1986—is still important reading. A similar workshop in the United States in 1978 on the fall in coronary heart disease mortality first focused American and world attention on the need to evaluate the factors responsible for the decline in deaths from coronary heart disease seen in the United States from 1968. By 1985 there had been a decline of 60%.

This book has 30 short papers relating to time trends and regional patterns of coronary heart disease and medical care, determinants of mortality from coronary heart disease, the influence of medical care on risk factors, management of acute myocardial infarction in and out of hospital, and the influence of medical care on chronic coronary disease. The standard of presentation is high although it is frustrating to realise that there are no references beyond 1986. Surely the editors of this type of book should not only allow but insist on each paper carrying an additional annotated bibliography of the major new papers on the subject appearing between the meeting and the reading of proofs. Many of the reports making up the chapters have appeared in print since the 1986 meeting, but the coming together of all these presentations in a well edited format makes for a structured approach to the overall problem.

Britain is seeing a small but regular decline in deaths from coronary heart disease since about 1976. There is currently a heightened concern about the allocation of resources to prevention (£10 million) and treatment (£500 million) and an urgent need to evaluate the impact on the morbidity and mortality of coronary heart disease of various preventive and therapeutic (medical and surgical) measures. This book provides a very useful primer for all those embarking on the new phase on coronary heart disease in Britain. By American standards it may be dated, but it reaches Britain before we have established a comprehensive national system for monitoring risk factors and before we have evaluated the true need for the various surgical procedures currently available. At a time when the health care system is changing in unpredictable ways, we might do well to learn from the endeavours of others. Epidemiological surveillance needs to be adapted to track rapidly evolving care for patients with coronary heart disease. The new therapeutic methods require new and efficient clinical trials to justify their use. Diagnostic methods need to be evaluated because their costs and implications are considerable. While death rates from coronary heart disease in Britain will probably continue to decline slowly, we remain high in the world league table and we need to know how to evaluate the factors responsible for this fall in order to increase the rate by appropriate measures. This book should be read and considered by all those participating in the current coronary heart disease campaigns.

A G SHAPER

References

1 Committee of Public Accounts. *Twenty sixth report: coronary heart disease*. London: HMSO, 1989.
2 King's Fund Forum Consensus statement. Blood cholesterol measurement in the prevention of coronary heart disease. London: King's Fund Centre, 1989.

Br Heart J 1989;62:489–92

Correspondence

Prognostic significance of programmed ventricular stimulation in survivors of acute myocardial infarction

Sir,
We were most interested in the paper by Bhandari *et al* (1989;61:410–6) because we are engaged in a similar study. There are several points upon which we would like to comment.

Firstly, 10 out of 33 patients with inducible sustained arrhythmias were treated with potent antiarrhythmic agents. Though the drugs were chosen empirically and later stopped, the fact remains that several patients may have been protected from arrhythmic events during the high risk early post-infarction phase. Even if outcome was influenced in only a small number of patients, this could have significantly influenced the overall results, because there were only a small number of end points.

Secondly, as Bhandari *et al* themselves confirmed, inducible ventricular fibrillation is known to be a non-specific response to ventricular stimulation[1] and should not be included as a positive response in the overall analysis. Inducible ventricular tachycardia was, in fact, present in all but one of their patients who died suddenly. The predictive accuracy of inducible ventricular tachycardia is also known to be greater if only uniform ventricular tachycardia is regarded as important—particularly if an upper rate limit (for example < 250 beats per minute) is included.[2]

Thirdly, it should be further emphasised that Bhandari *et al's* study included only patients who were at a relatively low risk of arrhythmic events (Killip class I or II). Most patients with documented spontaneous ventricular arrhythmias after infarction have significantly impaired left ventricular function. Arrhythmias may occur either as a primary electrical phenomenon or as the result of new ischaemic events; perhaps the latter are a more likely cause in those with small infarcts.

Finally, follow up was as short as four months in some patients, though sudden deaths occurred as late as 26 months. The predictive accuracy of the test may increase with longer follow up.

Our preliminary results from 75 unselected patients including those with clinical evidence of major infarction tested with up to three extrastimuli[3] show a higher sensitivity (6/6) and positive predictive accuracy (6/8) than in the study of Bhandari *et al*, in line with previous studies that included high risk patients.[4,5] We found a high incidence (29%, 22 patients) of sustained inducible arrhythmias, often of a non-specific multiform type requiring DC cardioversion, which makes the test invasive and therefore unattractive.

We agree that programmed ventricular stimulation should not be used as a test in the routine assessment of patients after uncomplicated infarction. It may be useful, however, in the identification and selection of treatment in those judged on clinical and non-invasive grounds to be at high risk of death from arrhythmia, and of course in patients with late spontaneous sustained ventricular tachycardia, in whom empirical treatment may be ineffective and is possibly harmful.

T R Cripps,
T G Farrell,
A J Camm,
D E Ward,
Department of Cardiological Sciences,
St George's Hospital Medical School,
Cranmer Terrace,
Tooting,
London SW17 0RE.

References

1 Brugada P, Green M, Abdollah H, Wellens H. Significance of ventricular arrhythmias initiated by programmed extrastimulation. The importance of the type of ventricular arrhythmia induced and the number of premature stimuli required. *Circulation* 1984; 69:87–92.

2 Breithardt G, Borggrefe M, Martınez-Rubio A, Podczeck A. Prognostic significance of ventricular late potentials in the post-myocardial infarction period. *Herz* 1988;13:180–7.

3 Cripps T, Bennett ED, Camm AJ, Ward DE. Inducibility of sustained monomorphic ventricular tachycardia as a prognostic indicator in survivors of recent myocardial infarction: a prospective evaluation in relation to other prognostic variables. *J Am Coll Cardiol* 1989;14:289–96.

4 Richards D, Cody D, Denniss A, Russell P, Young A, Uther J. Ventricular electrical instability: a predictor of death after myocardial infarction. *Am J Cardiol* 1983;51:75–80.

5 Waspe E, Seinfeld D, Kim SG, Matos JA, Fisher JD. Prediction of sudden death and spontaneous ventricular tachycardia in survivors of uncomplicated myocardial infarction: value of the response to programmed stimulation using a maximum of three ventricular extrastimuli. *J Am Coll Cardiol* 1985; 5:1292–301.

This letter was shown to the authors, who reply as follows:

Sir,

As Dr Cripps and his colleagues note (and as we emphasised in our article) the results of our study are applicable only to clinically stable patients with uncomplicated myocardial infarctions and the finding ought not be extrapolated to patients with complicated infarctions where the risk of future arrhythmic events is higher and the predictive accuracy of programmed ventricular stimulation may be better. Their study[1] and others including our own,[2-4] support the clinical use of programmed ventricular stimulation in such patients.

Until recently there were few data on the clinical significance of inducible ventricular fibrillation in survivors of acute myocardial infarction. The results of our study and those of Denniss *et al*[3] clearly show that inducible ventricular fibrillation is a non-specific response of little clinical significance in these patients. Therefore we agree that this arrhythmia should not be included as a positive end point in existing or future prospective trials of programmed stimulation in survivors of recent myocardial infarction.

In our article we commented on the limitations imposed by the empirical antiarrhythmic treatment started in our first 10 patients with inducible sustained ventricular arrhythmias. The minimum length of follow up was at least 12 months in all but five patients, who were lost to follow up between four and eight months after the index infarction.

A K Bhandari
Los Angeles Cardiology Associates,
1245 Wilshire Boulevard,
Suite 606,
Los Angeles, CA 90017,
USA

References

1 Cripps TR, Bennett ED, Camm AJ, Ward DE. Inducibility of sustained monomorphic ventricular tachycardia as a prognostic indicator in survivors of recent myocardial infarction: A prospective evaluation in relation to other variables. *J Am Coll Cardiol* 1989;14:289–96.

2 Waspe LE, Seinfeld D, Ferrer A, *et al.* Prediction of sudden death and spontaneous ventricular tachycardia in survivors of complicated myocardial infarction: Value of the response to programmed stimulation using a maximum of three ventricular extrastimuli. *J Am Coll Cardiol* 1985;5:1292–301.

3 Denniss AR, Richarde DA, Cody DV, *et al.* Prognostic significance of ventricular tachycardia and fibrillation induced at programmed stimulation and delayed potentials detected on the signal averaged electrocardiograms of survivors of acute myocardial infarction. *Circulation* 1985;74:731–45.

4 Bhandari A, Hong R, Kotlewski A, Rubin J, McIntosh N, Rahimtoola SH. Prognostic significance of programmed stimulation in high risk patients surviving acute myocardial infarction [Abstract]. *J Am Coll Cardiol* 1988;11:6.

Timing of treatment with oxygen radical scavengers and its influence on reperfusion injury

Sir,

In their editorial on oxygen radicals and myocardial damage (1989;**61**:4–8), Burrell and Blake pointed out that proof that there is specific, reperfusion-mediated damage depends on the administration of oxygen radical scavengers at the moment of reperfusion rather than before the onset of ischaemia. This is a valid point, but the reader may be left with the impression that the hypothesis of a specific reflow injury remains to be tested because the editorial does not refer to the results of several pertinent published reports.

In the classic study by Jolly *et al*, administration of superoxide dismutase and catalase towards the end of the ischaemic period proved as effective in reducing infarct size as pretreatment.[1] Furthermore, in other studies administration of "anti-free radical" agents at the moment of reflow, *after* the ischaemic episode, considerably reduced the myocardial concentration of oxygen radicals,[2] improved recovery of energy metabolism[3 4] and of contractile function in isolated hearts[3 4] and in anaesthetised dogs,[5] and reduced infarct size in a long term canine model of coronary artery occlusion and reperfusion.[6]

Thus although the issue is not yet settled,[7-9] there seems to be substantial evidence to indicate that, under certain circumstances, oxygen radicals can induce specific myocardial damage, which is separate from ischaemic damage, in various experimental models of post-ischaemic reperfusion. The studies that I draw attention to go some way to proving that scavengers of oxygen radicals given at the moment of reperfusion are effective in countering this specific myocardial damage.

Giuseppe Ambrosio,
Division of Cardiology,
2nd School of Medicine,
University of Naples,
Via Sergio Pansini 5,
80131 Naples,
Italy.

References

1 Jolly SR, Kane WJ, Bailie MB, Abrams GD, Lucchesi BR. Canine myocardial reperfusion injury. Its reduction by the combined administration of superoxide dismutase and catalase. *Circ Res* 1984;54:277–85.
2 Zweier JL, Rayburn BK, Flaherty JT, Weisfeldt ML. Recombinant superoxide dismutase reduces oxygen free radical concentrations in reperfused myocardium. *J Clin Invest* 1987;80:1728–34.
3 Ambrosio G, Weisfeldt ML, Jacobus WE, Flaherty JT. Evidence for a reversible oxygen radical-mediated component of reperfusion injury: reduction by recombinant human superoxide dismutase administered at the time of reflow. *Circulation* 1987;75:282–91.
4 Ambrosio G, Zweier JL, Jacobus WE, Weisfeldt ML, Flaherty JT. Improvement of post-ischaemic myocardial function and metabolism by administration of deferoxamine at the time of reflow: the role of iron in the pathogenesis of reperfusion injury. *Circulation* 1987;76:906–15.
5 Bolli R, Patel BS, Jeroudi MO, Lai EK, McCay PB. Demonstration of free radical generation in "stunned" myocardium of intact dogs with the use of the spin trap alpha-phenyl N-tert-butyl nitrone. *J Clin Invest* 1988; 88:476–85.
6 Ambrosio G, Becker LC, Hutchins GM, Weisman HF, Weisfeldt ML. Reduction in experimental infarct size by recombinant human superoxide dismutase: insights into the pathophysiology of reperfusion injury. *Circulation* 1986;74:1424–33.
7 Richards VJ, Murry CE, Jennings RB, Reimer KA. Therapy to reduce free radicals during early reperfusion does not limit the size of myocardial infarcts caused by 90 min of ischemia in dogs. *Circulation* 1988;78:473–80.
8 Przyklenk K, Kloner RA. "Reperfusion injury" by oxygen free radicals? Effect of superoxide dismutase plus catalase, given at the time of reperfusion, on myocardial infarct size, contractile function, coronary microvasculature, and regional myocardial blood flow. *Circ Res* 1989;64:86–96.
9 Nejima J, Knight DR, Fallon JT, *et al.* Superoxide dismutase reduces reperfusion arrhythmias but fails to salvage regional function or myocardium at risk in conscious dogs. *Circulation* 1989;79:143–53.

This letter was shown to the authors, who reply as follows:

Sir,

The results of many studies confirm the occurrence of a reperfusion event associated with the formation of oxygen free radicals in animals.[1] There is similarly convincing evidence that in the animal heart this event is associated with myocardial injury and that the extent of this injury may be modified by agents altering free radical mechanisms.[2] The optimal timing for such therapeutic intervention remains open to debate, but certainly some benefit may be achieved from treatment given after the ischaemic period.

However, small animals may be particularly susceptible to oxidative stress,[3 4] and therefore more likely to benefit from antioxidant treatment, and the applicability of animal studies to patients with acute myocardial infarction is in some doubt.

From a practical point of view, long term prophylactic treatment for patients at risk of infarction with agents such as allopurinol seems unlikely to become widely established even if a small benefit were shown, and the potential beneficial effects of free radicals[5] may be jeopardised by such treatment. An "anti-free radical" cocktail administered at the same time as a thrombolytic agent (that is after the ischaemic period, immediately before reperfusion) is the most promising starting point, and we agree with Ambrosio that any evidence that this may be beneficial in animals[6 7] is encouraging. However, this does not alter our conclusion that therapeutic trials are not justified without further elucidation of free radical interactions in humans (1989;**61**:4–8).

C J Burrell,
D R Blake,
Cardiac Department,
The London Hospital,
Whitechapel,
London E1 1BB.

References

1 Granger DN, Hollwarth ME, Parks DA. Ischaemia-reperfusion injury: role of oxygen-derived free radicals. *Acta Physiol Scand* 1986;**548**:47–63.

2 Hearse DJ, Yellon DM, eds. *Therapeutic approaches to myocardial infarct size limitation.* New York: Raven Press, 1984.

3 Parke DV. *Mechanisms of chemical toxicity – a unifying hypothesis.* London: Academic Press, 1982:267–84.

4 Halliwell B, Gutteridge JMC. *Free radicals in biology and medicine.* Oxford: Oxford University Press, 1989.

5 Murrell GAC, Francis MJO, Bromley L. Free radicals and Dupuytren's contracture *Br Med J* 1987; **295**:1373–5.

6 Ambrosio G, Becker LC, Hutchins GM, *et al.* Reduction in experimental infarct size by recombinant human superoxide dismutase: insights into the pathophysiology of reperfusion injury. *Circulation* 1986; **74**:1424–33.

7 Ambrosio G, Zweier JL, Jacobus WE, *et al.* Improvement in postischaemic myocardial function and metabolism induced by administration of deferoxamine at the time of reflow: the role of iron in the pathogenesis of reperfusion injury. *Circulation* 1987;**76**:906–15.

Notices

British Cardiac Society

The Annual General Meeting will take place at the English Riviera Centre, Torquay on 22 to 25 May 1990. The closing date for receipt of abstracts is 19 January 1990.

Advances in diagnostic and therapeutic cardiac catheterization

A meeting entitled Advances in Diagnostic and Therapeutic Cardiac Catheterization, organised by Dr Carl J Pepine, will take place at the Peabody Orlando, Orlando, Florida on 16 to 18 February 1990. Further information from Margaret Sgro, Extramural Programs Department, American College of Cardiology, 9111 Old Georgetown Road, Bethesda, MD 20814, USA.

Hyperlipidemia in childhood and the development of atherosclerosis

A meeting on Hyperlipidemia in Childhood and the Development of Atherosclerosis sponsored by The New York Academy of Sciences will take place at the Hyatt Regency, Bethesda, Maryland on 2 to 4 May 1990. Further information from the Conference Department, The New York Academy of Sciences, 2 East 63rd Street, New York, NY 10021, USA.

AUTHOR INDEX

1989, Volume 62

Abdulla A K *see* Mohiaddin R H *et al*
Agata Y *see* Hiraishi S *et al*
Ahsan A *see* Rowland E *et al*
Allen K M (& Wharton J, Polak J M, Haworth S G) A study of nerves containing peptides in the pulmonary vasculature of healthy infants and children and of those with pulmonary hypertension 353
Amano K *see* Shiota T *et al*
Ambrosio G Timing of treatment with oxygen radical scavengers and its influence on reperfusion injury correspondence 490
Anderson A J *see* Freedman D S *et al*
Anderson R H *see* Baker E J *et al*
Fong L V *et al*
Angelo-Nielsen K *see* Svanegaard J *et al*
Angelsen B A J *see* Samstad S O *et al*
Arisawa J (& Morimoto S, Ikezoe J, Hamada S, Kozuka T, Sano T, Ogawa M, Matsuda H, Kawashima Y) Cross sectional echocardiographic anatomy of common atrioventricular valve in atrial isomerism 291
Aylward P E (& Russell A E, Smith S A, Sheppard J M, Stoner J E) Changes in transmitral velocities with heart rate. correspondence reply 415
Ayton V *see* Baker E J *et al*
Azar A J *see* Deckers J W *et al*

Bailey L *see* Chamberlain D *et al*
Bain R J I *see* Tan L B *et al*
Baker E J (& Ayton V, Smith M A, Parsons J M, Maisey M N, Ladusans E J, Anderson R H, Tynan M, Yates A K, Deverall P B) Magnetic resonance imaging of coarctation of the aorta in infants: use of a high field strength 97. Magnetic resonance imaging at a high field strength of ventricular septal defects in infants 305
Balaji J *see* Sutherland G R *et al*
Balakrishnan K G *see* Gupta P N *et al*
Balcon R *see* Lyons J *et al*
Norell M S *et al*
Skehan J D *et al*
Ballantyne D *see* Chamberlain D *et al*
Bamber J C *see* Massay R J *et al*
Banner N R *see* Hausdorf G *et al*
Barboriak J J *see* Freedman D S *et al*
Behan P O *see* Behan W M H *et al*
Behan W M H (& Behan P O, Reid J M, Doig W, Gairns J) Family studies of congenital heart block associated with Ro antibody 320
Belder M de *see* de Belder M
Bennett D H (& Coyle C) Development of multiform ventricular tachycardia during atrioventricular nodal reentrant tachycardia case report 220
Benraad Th J *see* Tan A C I T L *et al*
Benson L N *see* Vogel M *et al*
Bhamra R *see* Till J A *et al*
Bhandari A K Prognostic significance of programmed ventricular stimulation in survivors of acute myocardial infarction: correspondence reply 490
Blake D R *see* Burrell C J & Blake D R
Bogren H G *see* Mohiaddin R H *et al*
Bonarjee V *see* Haugeberg G *et al*
Book Reviews
  Higgins M W (& Luepker R V) editors: Trends in coronary heart disease mortality The influence of medical care 1988 488
  Segall H N Canadian cardiology. Pioneers of cardiology in Canada 1820–1970: the genesis of Canadian cardiology 1988 78
  Ward M P (& Milledge J S, West J B) High altitude medicine and physiology 1989 236
Boyle D McC *see* Chamberlain D *et al*
Brooks N H *see* Jones M *et al*
Burden A C *see* Woods K L *et al*
Burrell C J (& Blake D R) Timing of treatment with oxygen radical scavengers and its influence on reperfusion injury· correspondence reply 491
Burrows P *see* Vogel M *et al*

Cameron J S *see* Raftery M J *et al*
Camm A J *see* Cripps T R *et al*
Caplin J L (& Flatman W D, Dyke L, Wiseman M N, Dymond D S) Influence of respiratory variations on right ventricular function 253
Carey C *see* Griffith M J *et al*
Skehan J D *et al*
Caruana M P *see* Rodrigues E A *et al*
Castelli G *see* Ciaccheri M *et al*
Cecchi F *see* Ciaccheri M *et al*
Chamberlain D (& Bailey L, Sowton E, Ballantyne D, Boyle D McC, Oliver M) Staffing in cardiology in the United Kingdom 1988 fifth biennial survey 482
Chambers J (& Monaghan M, Jackson G) Colour flow Doppler mapping in the assessment of prosthetic valve regurgitation 1
Chamsi-Pasha H *see* Thomson D *et al*
Channer K S (& Jones J V) Changes in transmitral velocities with heart rate· correspondence 415
Chong E *see* Rankin A C *et al*
Christopher B *see* Nash G B *et al*
Ciaccheri M (& Castelli G, Cecchi F, Nannini M, Santoro G, Troiani V, Zuppiroli A, Dolara A) Lack of correlation between intracavitary thrombosis detected by cross sectional echocardiography and systemic emboli in patients with dilated cardiomyopathy 26
Clarke B *see* Till J *et al*
Cobbe S M *see* Rankin A C *et al*
Coleman E N *see* Houston A B *et al*
Coltart D J *see* Griffith M J *et al*
Conroy R M *see* Robinson K *et al*
Conway N *see* Smyllie J *et al*
Correction 240, 328
Corten P M J *see* Tan A C I T L *et al*
Coyle C *see* Bennett D H & Coyle C
Crean P A *see* Gibbs J S R *et al*
Cripps T R (& Farrell T G, Camm A J, Ward D E) Prognostic significance of programmed ventricular stimulation in survivors of acute myocardial infarction. correspondence 489
Cross J H (& De Giovanni J V, Silove E D) Use of streptokinase to aid in drainage of postoperative pericardial effusion· case report 217
Cunningham S *see* Gibbs J S R *et al*
Rowland E *et al*

Daniels O *see* de Knecht S *et al*
Dark J F *see* Jones M *et al*
Davies S *see* Lyons J *et al*
Dawkins K *see* Smyllie J *et al*
de Belder M *see* Skehan J D *et al*
de Giovanni J V *see* Cross J H *et al*
de Knecht S (& Hopman J C W, Daniels O, Stoelinga G B A, Reneman R S, Hoeks A P G) Assessment of the orifice diameter by a multigated pulsed Doppler system in children with congenital semilunar valve stenosis 50
Deckers J W (& Rensing B J, Tijssen J G P, Vinke R V H, Azar A J, Simoons M L) A comparison of methods of analysing exercise

tests for diagnosis of coronary artery disease 438
Deiraniya A K *see* Jones M *et al*
Deverall P B *see* Baker E J *et al*
Dickstein K *see* Haugeberg G *et al*
Doig W *see* Behan W M H *et al*
Doig W B *see* Houston A B *et al*
    Lim M K *et al*
Dolara A *see* Ciaccheri M *et al*
Dormandy J A *see* Nash G B *et al*
Dyke L *see* Caplin J L *et al*
Dymond D S *see* Caplin J L *et al*

Emaneulsson H *see* Mannheimer C *et al*
Ewing D J *see* McAreavey D *et al*

Faergeman O *see* Vigholt-Sørensen E *et al*
Fagg N L K *see* Baker E J *et al*
Farrell T G *see* Cripps T R *et al*
Feld H (& Roth J) Severe haemolytic anaemia after replacement of the mitral valve by a St Jude medical prosthesis: case report 475
Finley J P *see* Giddins N G *et al*
Firmin D N *see* Mohiaddin R H *et al*
Flatman W D *see* Caplin J L *et al*
Fong L V (& Anderson R H, Siewers R D, Trento A, Park S C) Anomalous origin of one pulmonary artery from the ascending aorta. a review of echocardiographic catheter, and morphological features 389
Fox K M *see* Gibbs J S R *et al*
Fraser A G *see* Lewis N P *et al*
Freedman D S (& Gruchow H W, Walker J A, Jacobsen S J, Anderson A J, Sobocinski K A, Barboriak J J) Cigarette smoking and non-fatal myocardial infarction in women. is the relation independent of coronary artery disease? 273
Freedom R M *see* Vogel M *et al*
Fujino N *see* Hiraishi S *et al*

Gairns J *see* Behan W M H *et al*
Gardener J *see* Lyons J *et al*
Gardener J E *see* Norell M S *et al*
Ghosh M K *see* Gupta P N *et al*
Gialafos J (& Theophilis A, Siamas G) Spontaneous displacement of a pacemaker electrode and its subsequent successful re-implantation. case report 403
Gibbs J S R (& Crean P A, Mockus L, Wright C, Sutton G C, Fox K M) The variable effects of angiotensin converting enzyme inhibition on myocardial ischaemia in chronic stable angina 112
—(& Cunningham D, Shapiro L M, Park A, Poole-Wilson P A, Fox K M) Diurnal variation of pulmonary artery pressure in chronic heart failure 30
Gibson D G *see* Massay R J *et al*
    Morgan J M *et al*
    Ng K S K & Gibson D G
    Redington A N *et al*
Giddins N G (& Finley J P, Nanton M A, Roy D L) The natural course of supravalvar aortic stenosis and peripheral pulmonary artery stenosis in Williams's syndrome 315
Giovanni J V de *see* De Giovanni J V
Gnanapragasam J *see* Houston A B *et al*
Gnanapragasam J P (& Houston A B, Lilley S) Congenital fistula between the left ventricle and coronary sinus: elucidation by colour Doppler flow mapping: case report 406
Godman M J *see* Shaw N J *et al*
Gosalakkal J A (& Sugrue D D) Malignant melanoma of the right atrium: antemortem diagnosis by transvenous biopsy: case report 159
Goudevenos J (& Parry G, Morritt G N) Subacute rupture of a pseudoaneurysm formed by late rupture of a true left ventricular aneurysm: case report 225
Griffith M J (& Carey C, Coltart D J, Jenkins B S, Webb-Peploe M M) Inaccuracies in using aortic valve gradients alone to grade severity of aortic stenosis 372
Gruchow H W *see* Freedman D S *et al*
Gupta P N (& Valiathan M S, Balakrishnan K G, Kartha C C, Ghosh M K) Clinical course of endomyocardial fibrosis 450

Hada Y *see* Shiota T *et al*
Haga P *see* Till J A *et al*
Hamada S *see* Arisawa J *et al*
Hansen J S *see* Svanegaard J *et al*
Harringer W *see* Schutzenberger W *et al*
Hasegawa I *see* Shiota T *et al*
Hasleton P *see* Thomson D *et al*
Hatle L *see* Samstad S O *et al*
Haugeberg G (& Bonarjee V, Dickstein K) Fatal intrathoracic haemorrhage after cardiopulmonary resuscitation and treatment with streptokinase and heparin. case report 157
Haupt H-M *see* Neumann F-J *et al*
Hausdorf G (& Banner N R, Mitchell A, Khaghani A, Martin M, Yacoub M) Diastolic function after cardiac and heart-lung transplantation 123
Haworth S G *see* Allen K M *et al*
Hayes A *see* Shaw N J *et al*
Hayward R *see* Taggart P *et al*
Henderson R A The Randomised Intervention Treatment of Angina (RITA) Trial protocol: a long term study of coronary angioplasty and coronary artery bypass surgery in patients with angina British cardiology 411
Herbinger W *see* Schutzenberger W *et al*
Hilton C J *see* McComb J M *et al*
Hiraishi S (& Fujino N, Saito K, Oguchi K, Kadoi N, Agata Y, Horiguchi Y, Hozumi H, Yashiro K) Responsiveness of the ductus arteriosus to prostaglandin E_1 assessed by combined cross sectional and pulsed Doppler echocardiography 140
Hodsman G P *see* Phillips P A *et al*
Hoeks A P G *see* de Knecht S *et al*
Holt D W *see* Till J A *et al*
Hopman J C W *see* de Knecht S *et al*
Horiguchi Y *see* Hiraishi S *et al*
Hossack K F (& Tewksbury J C, Reid L M) Successful repair of an atrial septal defect associated with right to left shunting: case report 69
Houston A B (& Lim M K, Doig W B, Gnanapragasam J, Coleman E N, Jamieson M P G, Pollock J C S) Doppler flow characteristics in the assessment of pulmonary artery pressure in ductus arteriosus 284
see also Gnanapragasam J P *et al*
    Lim M KM *et al*
    Reid J M *et al*
Hozumi H *see* Hiraishi S *et al*
Hunter E *see* McCrea W A *et al*

Ikezoe J *see* Arisawa J *et al*
Imai Y *see* Isomatsu Y *et al*
Isomatsu Y (& Kurosawa H, Imai Y) Straddling tricuspid valve without a ventricular septal defect: case report 222

Jackson G *see* Chambers J *et al*
Jacobs H S *see* Rodrigues E A *et al*
Jacobsen S J *see* Freedman D S *et al*
Jamieson M P G *see* Houston A B *et al*
Jenkins B S *see* Griffith M J *et al*
Johansen E *see* Samstad S O *et al*
John R *see* Taggart P *et al*
Johnston A *see* Till J A *et al*
Johnston C I *see* Phillips P A *et al*
Jones J V *see* Channer K S & Jones J V
Jones M (& Schofield P M, Brooks N H, Dark J F, Moussalli H, Deiraniya A K, Lawson R A M, Rahman A N) Aortic valve replacement with combined myocardial revascularisation 9

Kadoi N *see* Hiraishi S *et al*

Kartha C C *see* Gupta P N *et al*

Kawashima Y *see* Arisawa J *et al*

Keeton B R *see* Sutherland G R *et al*

Kerschner K *see* Schutzenberger W *et al*

Khaghani A *see* Hausdorf G *et al*

Klipstein R H *see* Mohiaddin R H *et al*

Kloppenborg P W C *see* Tan A C I T L *et al*

Knecht S de *see* de Knecht S

Knight W B Hypoplastic right retro-oesophageal aortic arch similarities to interrupted aortic arch. case report 477

Koffman G *see* Raftery M J *et al*

Kozuka T *see* Arisawa J *et al*

Krikler D M The roots of modern British cardiology 230

Kristoffersen K *see* Samstad S O *et al*

Kubler W *see* Neumann F-J *et al*

Kurosawa H *see* Isomatsu Y *et al*

Ladusans E J *see* Baker E J *et al*
 Parsons J M *et al*
 Qureshi S A *et al*

Lahiri A (& Raftery E B) Radionuclide measurements of diastolic function for assessing early left ventricular abnormalities in the hypertensive patient. correspondence reply 237
 see also Rodrigues E A *et al*

Lamfers E J P *see* Tan A C I T L *et al*

Langleben D Pulmonary capillary haemangiomatosis: correspondence 239

Lawson R A M *see* Jones M *et al*

Layton C *see* Lyons J *et al*

Layton C A *see* Norell M S *et al*

Leach I H *see* Murphy J J & Leach I H

Leisch F *see* Schutzenberger W *et al*

Lewis N P (& Williams G T, Fraser A G) Unusual and intraoperative epicardial echocardiographic features of a papillary tumour of the aortic valve case report 470

Lilley S *see* Gnanapragasam J P *et al*

Lilley S *see* Lim M K *et al*

Lim M K (& Houston A B, Doig W B, Lilley S, Murtagh E P) Variability of the Doppler gradient in pulmonary valve stenosis before and after balloon dilatation 212
 see also Houston A B *et al*

Limas C *see* Limas C J & Limas C

Limas C J (& Limas C) HLA antigens in idiopathic dilated cardiomyopathy 379

Linker D T *see* Samstad S O *et al*

Littler W A *see* Tan L B *et al*

Loenhout T T van *see* van Loenhout T T

Logan-Sinclair R B *see* Massay R J *et al*

Longmore D B *see* Mohiaddin R H *et al*

Lundmark E *see* Reid J M *et al*

Lyons J (& Norell M, Gardener J, Davies S, Balcon R, Layton C) Phase and amplitude analysis of exercise digital left ventriculograms in patients with coronary disease 102

Lyons J P *see* Norell M S *et al*

McAreavey D (& Neilson J M M, Ewing D J, Russell D C) Cardiac parasympathetic activity during the early hours of acute myocardial infarction 165

McComb J M (& Vincent R, Hilton C J) Recurrent ventricular tachycardia associated with anomalous left coronary artery from the pulmonary artery in a child managed by revascularisation and map-guided endocardial resection: case report 396

McCrea W A (& Hunter E, Wilson C) Integration of ambulance staff trained in cardiopulmonary resuscitation with a medical team providing prehospital coronary care 417

Maisey M N *see* Baker E J *et al*

Maleki M (& Manley J C) Venospastic phenomena of saphenous vein bypass grafts possible causes for unexplained postoperative recurrence of angina or early or late occlusion of vein bypass grafts: case report 57

Manley J C *see* Maleki M & Manley J C

Mannheimer C (& Emanuelsson H, Waagstein F, Wilhelmsson C) Influence of naloxone on the effects of high frequency transcutaneous electrical nerve stimulation in angina pectoris induced by atrial pacing 36

Martin M *see* Hausdorf G *et al*

Martin R P *see* Qureshi S A *et al*

Massay R J (& Logan-Sinclair R B, Bamber J C, Gibson D G) Quantitative effects of speckle reduction on cross sectional echocardiographic images 298

Matsuda H *see* Arisawa J *et al*

Mills P G *see* Skehan J D *et al*

Mitchell A *see* Hausdorf G *et al*

Mockus L *see* Gibbs J S R *et al*

Mohiaddin R H (& Firmin D N, Underwood S R, Abdulla A K, Klipstein R H, Rees R S O, Longmore D B) Chemical shift magnetic resonance imaging of human atheroma 81
 —(& Underwood S R, Bogren H G, Firmin D N, Klipstein R H, Rees R S O, Longmore D B) Regional aortic compliance studied by magnetic resonance imaging· the effects of age, training, and coronary artery disease 90

Monaghan M *see* Chambers J *et al*

Monro J L *see* Sutherland G R *et al*

Morgan J M (& Raposo L, Gibson D G) Cardiac involvement in Churg-Strauss syndrome shown by echocardiography 462

Morimoto S *see* Arisawa J *et al*

Morris A J R *see* Nash G B *et al*

Morritt G N *see* Goudevenos J *et al*

Moussalli H *see* Jones M *et al*

Movsesian M (& Wray R B) Postpartum myocardial infarction· case report 154

Mulcahy R *see* Robinson K *et al*

Murphy J J (& Leach I H) Findings at necropsy in the heart of a patient with anticardiolipin syndrome case report 61

Murtagh E P *see* Lim M K *et al*

Nabarro J D N *see* Rodrigues E A *et al*

Nannini M *see* Ciaccheri M *et al*

Nanton M A *see* Giddins N G *et al*

Nash G B (& Christopher B, Morris A J R, Dormandy J A) Changes in the flow properties of white blood cells after acute myocardial infarction 329

Neilson J M M *see* McAreavey D *et al*

Neumann F-J (& Tillmanns H, Roebruck P, Zimmermann R, Haupt H-M, Kubler W) Haemorrheological abnormalities in unstable angina pectoris: a relation independent of risk factor profile and angiographic severity 421

Ng K S K (& Gibson D G) Impairment of diastolic function by shortened filling period in severe left ventricular disease 246

Nielsen K Angelo *see* Angelo-Nielsen K

Norell M *see* Lyons J *et al*

Norell M S (& Lyons J P, Gardener J E, Layton C A, Balcon R) Protective effect of collateral vessels during coronary angioplasty 241
 see also Skehan J D *et al*

Northover B J Estimation of the risk of death during the first year after acute myocardial infarction from systolic time intervals during the first week 429

Ogawa M *see* Arisawa J *et al*

Ogilvie B C *see* Sutherland G R *et al*

Oguchi K *see* Hiraishi S *et al*

Oldershaw P *see* Redington A N *et al*

Oldroyd K G *see* Rankin A C *et al*

Oliver M *see* Chamberlain D *et al*

Oliver M F Crisis in cardiovascular research in Britain 325

Park A *see* Gibbs J S R *et al*

Park S C *see* Fong L V *et al*

Parry G *see* Goudevenos J *et al*
Parsons J M (& Ladusans E J, Qureshi S A) Balloon dilatation of a stenosed modified (polytetrafluoroethylene) Blalock-Taussig shunt: case report 228
——Growth of the pulmonary artery after neonatal balloon dilatation of the right ventricular outflow tract in an infant with the tetralogy of Fallot and atrioventricular septal defect: case report 65
see also Baker E J *et al*
Pasha H Chamsi- *see* Chamsi-Pasha H
Peploe M M Webb- *see* Webb-Peploe M M
Phillips P A (& Hodsman G P, Johnston C I) Plasma atrial natriuretic peptide in patients with acute myocardial infarction. effects of streptokinase: correspondence reply 238
Polak J M *see* Allen K M *et al*
Pollock J C S *see* Houston A B *et al*
Poole-Wilson P A *see* Gibbs J S R *et al*

Qureshi S A (& Ladusans E J, Martin R P) Dilatation with progressively larger balloons for severe stenosis of the pulmonary valve presenting in the late neonatal period and early infancy 311
see also Parsons J M *et al*

Rae A P *see* Rankin A C *et al*
Raftery E B *see* Lahiri A & Raftery E B
see also Rodrigues E A *et al*
Raftery M J (& Koffman G, Cameron J S) Calcific stenosis of a mitral valve xenograft in a patient in chronic renal failure case report 161
Rahman A N *see* Jones M *et al*
Ramsdale D R (& Schofield P M) Successful repeat percutaneous transluminal coronary angioplasty after failed coronary artery surgery for left main coronary artery dissection case report 400
Rankin A C (& Oldroyd K G, Chong E, Rae A P, Cobbe S M) Value and limitations of adenosine in the diagnosis and treatment of narrow and broad complex tachycardias 195
Raposo L *see* Morgan J M *et al*
Redington A N (& Rigby M L, Oldershaw P, Gibson D G, Shinebourne E A) Right ventricular function 10 years after the Mustard operation for transposition of the great arteries: analysis of size, shape, and wall motion 455
Rees R S O *see* Mohiaddin R H *et al*
Reid J M (& Houston A B, Lundmark E) Hypertrophic cardiomyopathy in identical twins 384
see also Behan W M H *et al*
Reid L M *see* Hossack K F *et al*
Reneman R S *see* de Knecht S *et al*
Rensing B J *see* Deckers J W *et al*
Rickards A *see* Rowland E *et al*
Rigby M L *see also* Redington A N *et al*
Till J *et al*
Robinson K (& Conroy R M, Mulcahy R) When does the risk of acute coronary heart disease in ex-smokers fall to that in non-smokers? A retrospective study of patients admitted to hospital with a first episode of myocardial infarction or unstable angina 16
Rodrigues E A (& Caruana M P, Lahiri A, Nabarro J D N, Jacobs H S, Raftery E B) Subclinical cardiac dysfunction in acromegaly. evidence for a specific disease of heart muscle 185
Roebruck P *see* Neumann F-J
Rossvoll O *see* Samstad S O *et al*
Roth J *see* Feld H & Roth J
Rowland E (& Cunningham D, Absan A, Rickards A) Transvenous ablation of atrioventricular conduction with a low energy power source 361
see also Till J *et al*
Till J A *et al*
Roy D L *see* Giddins N G *et al*
Russell A E *see* Aylward P E *et al*
Russell D C *see* McAreavey D *et al*

Saito K *see* Hiraishi S *et al*
Sakamoto T *see* Shiota T *et al*
Samanta A *see* Woods K L *et al*
Samstad S O (& Torp H G, Linker D T, Rossvoll O, Skjaerpe T, Johansen E, Kristoffersen K, Angelsen B A J, Hatle L) Cross sectional early mitral flow velocity profiles from colour Doppler 177
Sano T *see* Arisawa J *et al*
Santoro G *see* Ciaccheri M *et al*
Schneeweiss A Radionuclide measurements of diastolic function for assessing early left ventricular abnormalities in the hypertensive patient: correspondence 237
Schonfield J *see* Tinker A *et al*
Schofield P M *see* Jones M *et al*
Ramsdale D R & Schofield P M
Schutzenberger W (& Leisch F, Kerschner K, Harringer W, Herbinger W) Clinical efficacy of intravenous amiodarone in the short term treatment of recurrent sustained ventricular tachycardia and ventricular fibrillation 367
Shapiro L M *see* Gibbs J S R *et al*
Shaw N J (& Godman M J, Hayes A, Sutherland G R) Superior QRS axis in ventricular septal defect 281
Sheppard J M *see* Aylward P E *et al*
Shinebourne E A *see* Reddington A N *et al*
Till J *et al*
Till J A *et al*
Shiota T (& Sakamoto T, Takenaka K, Amano K, Hada Y, Hasegawa I, Suzuki J-I, Takahashi H, Sugimoto T) Aortic regurgitation associated with hypertrophic cardiomyopathy: a colour Doppler echocardiographic study 171
Siamas G *see* Gialafos J *et al*
Siewers R D *see* Fong L V *et al*
Silove E D *see* Cross J H *et al*
Simoons M L *see* Deckers J W *et al*
Sinclair R B Logan- *see* Logan-Sinclair R B
Skehan J D (& Carey C, Norrell M S, de Belder M, Balcon R, Mills P G) Patterns of coronary artery disease in post-infarction ventricular septal rupture 268
Skjaerpe T *see* Samstad S O *et al*
Smallhorn J F *see* Vogel M *et al*
Smith M A *see* Baker E J *et al*
Smith S A *see* Aylward P E *et al*
Smyllie J (& Dawkins K, Conway N, Sutherland G R) Diagnosis of ventricular septal rupture after myocardial infarction. value of colour flow mapping 260
Smyllie J H *see* Sutherland G R *et al*
Snow H M *see* Vigholt-Sørensen E *et al*
Sobocinski K A *see* Freedman D S *et al*
Sørensen E Vigholt *see* Vigholt-Sørensen E
Sowton E *see* Chamberlain D *et al*
Stoelinga G B A *see* de Knecht S *et al*
Stoner J E *see* Aylward P E *et al*
Sugimoto T *see* Shiota T *et al*
Sugrue D D *see* Gosalakkal J A & Sugrue D D
Sutherland G R (& Balaji S, Monro J L) Potential value of intraoperative Doppler colour flow mapping in operations for complex intracardiac shunting: case report 467
(& Smyllie J H, Ogilvie B C, Keeton B R) Colour flow imaging in the diagnosis of multiple ventricular septal defects 43
see also Shaw N J *et al*
Smyllie J *et al*
Sutton G C *see* Gibbs J S R *et al*
Sutton P *see* Taggart P *et al*
Suzuki J-I *see* Shiota T *et al*
Svanegaard J (& Angelo-Nielsen K, Hansen J S) Physiological hypertrophy of the heart and atrial natriuretic peptide during rest and exercise 445
Swanton H *see* Taggart P *et al*

Taggart P (& Sutton P, John R, Hayward R, Swanton H) The

epicardial electrogram: a quantitative assessment during balloon angioplasty incorporating monophasic action potentials recordings 342
TAKAHASHI H *see* Shiota T *et al*
TAKENAKA K *see* Shiota T *et al*
TAN A C I T L (& van Loenhout T T, Lamfers E J P, Corten P M J, Kloppenborg P W C, Benraad Th J) Plasma atrial natriuretic peptide in patients with acute myocardial infarction. effects of streptokinase: correspondence 238
TAN L B (& Bain R J I, Littler W A) Assessing cardiac pumping capability by exercise testing and inotropic stimulation 20
TEWKSBURY J C *see* Hossack K F *et al*
THEOPHILIS A *see* Gialafos J *et al*
THOMSON D (& Chamsi-Pasha H, Hasleton P) Heart transplantation for Churg-Strauss syndrome: case report 409
TIJSSEN J G P *see* Deckers J W *et al*
TILL J (& Shinebourne E A, Rigby M L, Clarke B, Ward D E, Rowland E) Efficacy and safety of adenosine in the treatment of supraventricular tachycardia in infants and children 204
TILL J A (& Shinebourne E A, Rowland E, Ward D E, Bhamra R, Haga P, Johnston A, Holt D W) Paediatric use of flecainide in supraventricular tachycardia clinical efficacy and pharmacokinetics 133
TILLMANNS H *see* Neumann F-J *et al*
TINKER A (& Uren N, Schofield J) Severe pulmonary hypertension in Ullrich-Noonan syndrome. case report 74
TORP H G *see* Samstad S O *et al*
TRENTO A *see* Fong L V *et al*
TROIANI V *see* Ciaccheri M *et al*
TYNAN M *see* Baker E J *et al*

UNDERWOOD S R *see* Mohiaddin R H *et al*
UREN N *see* Tinker A *et al*

VALIATHAN M S *see* Gupta P N *et al*
VAN LOENHOUT T T *see* Tan A C I T L *et al*
VIGHOLT-SØRENSEN E (& Faergeman O, Snow H M) Effects of xamoterol, a beta$_1$ adrenoceptor partial agonist, in patients with ischaemic dysfunction of the left ventricle 335
VINCENT R *see* McComb J M *et al*
VINKE R V H *see* Deckers J W *et al*
VOGEL M (& Benson L N, Burrows P, Smallhorn J F, Freedom R M) Balloon dilatation of congenital aortic valve stenosis in infants and children· short term and intermediate results 148

WAAGSTEIN F *see* Mannheimer C *et al*
WALKER J A *see* Freedman D S *et al*
WARD D E *see* Cripps T R *et al*
Till J *et al*
Till J A *et al*
WHARTON J *see* Allen K M *et al*
WILHELMSSON C *see* Mannheimer C *et al*
WILLIAMS G T *see* Lewis N P *et al*
WILSON C *see* McCrea W A *et al*
WILSON P A POOLE- *see* Poole-Wilson P A
WISEMAN M N *see* Caplin J L *et al*
WONG J S K Infective endocarditis in Crohn's disease. case report 163
WOODS K L (& Samanta A, Burden A C) Diabetes mellitus as a risk factor for acute myocardial infarction in Asians and Europeans 118
WRAY R B *see* Movsesian M A & Wray R B
WRIGHT C *see* Gibbs J S R *et al*

YACOUB M *see* Hausdorf G *et al*
YASHIRO K *see* Hiraishi S *et al*
YATES A K *see* Baker E J *et al*

ZIMMERMANN R *see* Neumann F-J *et al*
ZUPPIROLI A *see* Ciaccheri M *et al*

Br Heart J 1989;**61**:498–501

SUBJECT INDEX

1989, Volume 62

- Ablation, transvenous, of atrioventricular conduction with low energy power source (Rowland *et al*). 361
- Acromegaly, subclinical cardiac dysfunction, evidence for specific disease of heart muscle (Rodrigues *et al*) 185
- Adenosine
  - efficacy and safety in treatment of supraventricular tachycardia, infants and children (Till *et al*) 204
  - values and limitations in diagnosis and treatment of narrow and broad complex tachycardias (Rankin *et al*) 195
- Ambulance staff trained in cardiopulmonary resuscitation, integration with medical prehospital coronary care (McCrea *et al*) 417
- Amiodarone, intravenous, clinical efficacy in short term treatment of recurrent sustained ventricular tachycardia and ventricular fibrillation (Schutzenberger *et al*). 367
- Angina
  - chronic stable, with myocardial ischaemia, variable effects of angiotensin converting enzyme inhibition (Gibbs *et al*). 112
  - pectoris, unstable, haemorrheological abnormalities, independent of risk factors and severity (Neumann *et al*). 421
  - Randomised Intervention Treatment Trial protocol, long term study of coronary angioplasty and coronary artery bypass surgery; British cardiology (Henderson), 411
  - unstable, reduction of risk in ex-smokers (Robinson *et al*) 16
- Angiotensin converting enzyme inhibition, variable effects on myocardial ischaemia in chronic stable angina (Gibbs *et al*). 112
- Anticardiolipin syndrome, findings at necropsy in the heart (Murphy & Leach). 61
- Aortic arch, hypoplastic right retro-oesophageal, similarities to interrupted aortic arch, case report (Knight). 477
- Aortic
  - compliance, regional, studied by magnetic resonance imaging, effects of age, training, and coronary artery disease (Mohiaddin *et al*) 90
  - regurgitation associated with hypertrophic cardiomyopathy, colour Doppler echocardiographic study (Shiota *et al*). 171
  - stenosis, inaccuracies in using aortic valve gradients alone to grade severity (Griffith *et al*). 372
    - replacement with combined myocardial revascularisation (Jones *et al*) 9
    - stenosis, congenital, balloon dilatation, infants and children, short term and intermediate results (Vogel *et al*) 148
- Atheroma, human, chemical shift magnetic resonance imaging (Mohiaddin *et al*). 81
- Atrial
  - isomerism, cross sectional echocardiographic anatomy of common atrioventricular valve (Arisawa *et al*). 291
  - natriuretic peptide, and hypertrophy of heart, during rest and exercise (Svanegaard *et al*) 445
    - plasma, in myocardial infarction, effects of streptokinase. correspondence (Tan *et al*). 238
  - septal defect, successful repair, associated with right to left shunting (Hossack *et al*) 69
- Atrioventricular
  - conduction, transvenous ablation, with low energy power source (Rowland *et al*) 361
  - nodal reentrant tachycardia, multiform ventricular tachycardia development during: case report (Bennett & Coyle). 220
- Atrium, right, malignant melanoma, antemortem diagnosis by transvenous biopsy case report (Gosalakkal & Sugrue). 159

- Balloon dilatation *see* Percutaneous transluminal coronary angioplasty
- Blalock-Taussig shunt, modified, (polytetrafluoroethylene) balloon dilatation (Parsons *et al*). 228
- British Cardiac Society members and industry, relations between 235

- Calcific stenosis of mitral valve xenograft in chronic renal failure: case report (Raftery *et al*). 161
- Canadian cardiology. Pioneers of cardiology in Canada 1820–1970· book review (Segall) 78
- Cardiology
  - modern British, roots (Krikler) 230
  - staffing, United Kingdom 1988 (Chamberlain *et al*). 482
- Cardiomyopathy
  - hypertrophic, identical twins (Reid *et al*). 384
  - idiopathic dilated, and HLA antigens (Limas & Limas). 379
- Cardiopulmonary resuscitation and treatment with streptokinase and heparin, fatal intrathoracic haemorrhage after: case report (Haugeberg *et al*). 157
- Cardiovascular research crisis, Britain (Oliver). 325
- Churg-Strauss syndrome
  - cardiac involvement shown by echocardiography (Morgan *et al*). 462
  - heart transplantation for case report (Thomson *et al*) 409
- Cigarette smoking and non-fatal myocardial infarction in women, is relation independent of coronary artery disease? (Freedman *et al*). 273
- Coarctation of the aorta, magnetic resonance imaging, infants, use of high field strength (Baker *et al*) 97
- Collateral vessels, protective effect, during coronary angioplasty (Norell *et al*). 241
- Colour flow
  - imaging in diagnosis of multiple ventricular septal defects (Sutherland *et al*) 43
  - mapping value in diagnosis of ventricular septal rupture after myocardial infarction (Smyllie *et al*) 260
  - *see also* Doppler colour flow
- Common atrioventricular valve in atrial isomerism, cross sectional echocardiographic anatomy (Arisawa *et al*) 291
- Congenital heart block associated with Ro antibody (Behan *et al*). 320
- Coronary
  - artery disease, diagnosis, exercise tests, three methods compared (Deckers *et al*). 438
    - patterns in post-infarction ventricular septal rupture (Skehan *et al*) 268
    - phase-ventriculograms (Lyons *et al*) 102
    - and smoking, reduction of risk after giving up (Robinson *et al*) 16
  - care team, medical, integration with trained paramedics (McCrea *et al*). 417
- Corrections 240, 328
- Correspondence
  - Changes in transmitral velocities with heart rate (Channer & Jones) 415
  - Plasma atrial natriuretic peptide in patients with acute myocardial infarction: effects of streptokinase (Tan *et al*) 238
  - Prognostic significance of programmed ventricular stimulation in survivors of acute myocardial infarction (Cripps *et al*). 489
  - Pulmonary capillary haemangiomatosis (Langleben) 239
  - Radionuclide measurements of diastolic function for assessing early left ventricular abnormalities in the hypertensive patient (Schneeweiss) 237
  - Timing of treatment with oxygen radical scavengers and its influence on perfusion injury (Ambrosio) 490
- Crisis in cardiovascular research, Britain (Oliver). 325
- Crohn's disease with infective endocarditis: case report (Wong). 163

Cross sectional echocardiography
  anatomy of common atrioventricular valve in atrial isomerism (Arisawa *et al*). 291
  early mitral flow velocity profiles from colour Doppler (Samstad *et al*). 177
  images, quantitative effects of speckle reduction (Massay *et al*). 298

Diabetes mellitus as risk factor for myocardial infarction, Asians and Europeans (Woods *et al*) 118
Diastolic function
  after heart and heart-lung transplantation (Hausdorf *et al*) 123
  impairment by shortened filling period in severe left ventricular disease (Ng & Gibson). 246
Digital left ventriculograms, phase and amplitude analysis, coronary disease (Lyons *et al*) 102
Diurnal variation of pulmonary artery pressure in chronic heart failure (Gibbs *et al*) 30
Doppler colour flow mapping
  elucidation of congenital fistula between left ventricle and coronary sinus: case report (Gnanapragasam *et al*). 406
  intraoperative, value in complex intracardiac shunting operations: case report (Sutherland *et al*). 467
  prosthetic valve regurgitation (Chambers *et al*). 1
  pulmonary artery pressure in ductus arteriosus (Houston *et al*) 284
  gradient variability in pulmonary valve stenosis before and after balloon dilatation (Lim *et al*). 212
Ductus arteriosus
  pulmonary artery pressure, Doppler flow characteristics in assessment (Houston *et al*). 284
  responsiveness to prostaglandin E_1 assessed by combined cross sectional and pulsed Doppler echocardiography (Hiraishi *et al*) 140

Electrogram, epicardial, in assessment during balloon angioplasty incorporating monophasic action potentials recordings (Taggart *et al*) 342
Endomyocardial fibrosis, clinical course (Gupta *et al*) 450
Exercise
  tests, diagnosis of coronary artery disease, three methods compared (Deckers *et al*) 438
  testing and inotropic stimulation in assessing cardiac pumping capability (Tan *et al*) 20

Fistula, congenital, between left ventricle and coronary sinus, elucidation by colour Doppler flow mapping case report (Gnanapragasam *et al*). 406
Flecainide in supraventricular tachycardia, paediatric use, clinical efficacy and pharmacokinetics (Till *et al*) 133

Haemolytic anaemia, severe, after mitral valve replacement by St Jude medical prosthesis: case report (Feld & Roth) 475
Heart
  and heart-lung transplantation, diastolic function after (Hausdorf *et al*). 123
  failure, chronic, diurnal variation of pulmonary artery pressure (Gibbs *et al*). 30
  rate, changes in transmitral velocities correspondence (Channer & Jones) 415
  transplantation for Churg-Strauss syndrome case report (Thomson *et al*) 409
Heparin and streptokinase treatment, and cardiopulmonary resuscitation, fatal intrathoracic haemorrhage after; case report (Haugeberg *et al*) 157
HLA antigens in idiopathic dilated cardiomyopathy (Limas & Limas) 379
Hypertension
  pulmonary, study of nerves containing peptides, pulmonary vasculature, infants and children (Allen *et al*). 353
  radionuclide assessment of early left ventricular abnormalities: correspondence (Schneeweiss). 237
Hypertrophic cardiomyopathy, associated with aortic regurgitation, colour Doppler echocardiographic study (Shiota *et al*). 171
Hypertrophy of heart, and atrial natriuretic peptide, during rest and exercise (Svanegaard *et al*) 445
Hypoplastic right retro-oesophageal aortic arch, similarities to interrupted aortic arch. case report (Knight). 477

Infective endocarditis in Crohn's disease: case report (Wong) 163
Inotropic stimulation and exercise testing in assessing cardiac pumping capability (Tan *et al*) 20
Intracardiac shunting, intraoperative Doppler colour flow mapping case report (Sutherland *et al*) 467
Intrathoracic haemorrhage, fatal, after cardiopulmonary resuscitation and treatment with streptokinase and heparin. case report (Haugeberg *et al*) 157

Left main coronary artery dissection, successful balloon angioplasty after failed surgery. case report (Ramsdale & Schofield) 400

Magnetic resonance imaging
  chemical shift, of human atheroma (Mohiaddin *et al*). 81
  of coarction of the aorta, infants, use of high field strength (Baker *et al*) 97
  at high field strength of ventricular septal defects, infants (Baker *et al*). 305
  studying regional aortic compliance, effects of age, training, and coronary artery disease (Mohiaddin *et al*) 90
Map-guided endocardial resection, and revascularisation in recurrent ventricular tachycardia associated with anomalous left coronary artery from pulmonary artery: case report (McComb *et al*) 396
Melanoma, malignant, of right atrium, antemortem diagnosis by transvenous biopsy. case report (Gosalakkal & Sugrue) 159
Mitral
  flow velocity profiles, early, cross sectional, from colour Doppler (Samstad *et al*). 177
  valve replacement by St Jude medical prosthesis, severe haemolytic anaemia after case report (Feld & Roth) 475
    xenograft, calcific stenosis, in chronic renal failure: case report (Raftery *et al*) 161
Multiform ventricular tachycardia development during atrioventricular nodal reentrant tachycardia case report (Bennett & Coyle). 220
Multigated pulsed Doppler system in assessment of orifice diameter in children with congenital semilunar valve stenosis (de Knecht *et al*). 50
Mustard operation, transposition of great arteries, right ventricular function after 10 years (Redington *et al*) 455
Myocardial infarction
  cardiac parasympathetic activity during early hours (McAreavey *et al*) 165
  changes in flow properties of white blood cells after (Nash *et al*) 329
  diabetes mellitus as risk factor, Asians and Europeans (Woods *et al*). 118
  estimation of risk of death during first year from systolic time intervals during first week (Northover). 429
  non-fatal, and cigarette smoking in women, is relation independent of coronary artery disease? (Freedman *et al*) 273
  post-partum: case report (Movsesian & Wray). 154
  plasma atrial natriuretic peptide, effects of streptokinase. correspondence (Tan *et al*). 238
  prognostic significance of programmed ventricular stimulation correspondence (Cripps *et al*). 489
  reduction of risk in ex-smokers (Robinson *et al*). 16
  ventricular septal rupture after, colour flow mapping value in diagnosis (Smyllie *et al*) 260

- Myocardial ischaemia in chronic stable angina, variable effects of angiotensin converting enzyme inhibition (Gibbs *et al*) 112

- Naloxone influence on effects of high frequency transcutaneous electrical nerve stimulation (Mannheimer *et al*) 36
- Notices 80, 164, 240, 328, 416, 492

- Oxygen radical scavengers, treatment timing and influence on reperfusion injury. correspondence (Ambrosio) 490

- Pacemaker electrode, spontaneous displacement, and subsequent successful reimplantation: case report (Gialafos *et al*) 403
- Papillary tumour, aortic valve, unusual and intraoperative epicardial echocardiographic features case report (Lewis *et al*) 470
- Paramedics trained in cardiopulmonary resuscitation, integration with medical prehospital coronary care (McCrea *et al*) 417
- Parasympathetic activity, cardiac, during early hours of myocardial infarction (McAreavey *et al*) 165
- Peptides, nerves containing, in normal pulmonary vasculature in pulmonary hypertension, infants and children (Allen *et al*) 353
- Percutaneous transluminal coronary angioplasty
  - of congenital aortic valve stenosis, infants and children, short term and intermediate results (Vogel *et al*) 148
  - Doppler gradient variability in pulmonary valve stenosis before and after (Lim *et al*) 212
  - incorporating monophasic action potentials recordings, epicardial electrogram (Taggart *et al*). 342
  - neonatal, and growth of pulmonary artery· case report (Parsons *et al*) 65
  - with progressively larger balloons for severe stenosis of pulmonary valve (Qureshi *et al*) 311
  - protective effect of collateral vessels during (Norell *et al*) 241
  - of stenosed modified (polytetrafluoroethylene) Blalock-Taussig shunt· case report (Parsons *et al*) 228
  - successful repeat, after failed surgery: case report (Ramsdale & Schofield). 400
- Pericardial effusion, postoperative, streptokinase to aid drainage case report (Cross *et al*) 217
- Peripheral pulmonary artery stenosis, and supravalvar aortic stenosis in Williams's syndrome (Giddins *et al*). 315
- Postpartum myocardial infarction: case report (Movsesian & Wray) 154
- Programmed ventricular stimulation, myocardial infarction, prognostic significance. correspondence (Cripps *et al*). 489
- Prostaglandin E_1, ductus arteriosus responsiveness, assessed by combined cross sectional and pulsed Doppler echocardiography (Hiraishi *et al*) 140
- Prosthetic valve regurgitation, colour flow Doppler mapping in assessment (Chambers *et al*) 1
- Pseudoaneurysm, subacute rupture, formed by late rupture of true left ventricular aneurysm· case report (Goudevenos *et al*). 225
- Pulmonary
  - artery, anomalous origin, from ascending aorta, six patients (Fong *et al*). 389
    - pressure, diurnal variation in chronic heart failure (Gibbs *et al*). 30
      - in ductus arteriosus, Doppler flow characteristics in assessment (Houston *et al*) 284
  - capillary haemangiomatosis, formation of registry correspondence (Langleben). 239
- hypertension, severe, in Ullrich-Noonan syndrome (Tinker *et al*). 74
  - valve, stenosis, Doppler gradient variability before and after balloon dilatation (Lim *et al*). 212
    - severe, balloon dilatation with progressively larger balloons (Qureshi *et al*). 311
- Pumping, cardiac, assessing capability by exercise testing and inotropic stimulation (Tan *et al*) 20
- Radionuclide measurements of diastolic function for assessing early left ventricular abnormalities in hypertension correspondence (Schneeweiss). 237
- Randomised Intervention Treatment of Angina Trial protocol, long term study of coronary angioplasty and coronary artery bypass surgery: British cardiology (Henderson). 411
- Reperfusion injury, oxygen radical scavengers, treatment timing and influence. correspondence (Ambrosio) 490
- Respiratory variations influence on right ventricular function (Caplin *et al*). 253
- Revascularisation
  - combined myocardial, with aortic valve replacement (Jones *et al*). 9
  - and map-guided endocardial resection, in recurrent ventricular tachycardia associated with anomalous left coronary artery from pulmonary artery: case report (McComb *et al*). 396
- Right to left shunting associated with successful repair of atrial septal defect (Hossack *et al*) 69
- Ro antibody associated with congenital heart block (Behan *et al*). 320

- St Jude medical prosthesis for mitral valve replacement, severe haemolytic anaemia after (Feld & Roth) 475
- Saphenous vein bypass grafts, venospastic phenomena, angina recurrence or occlusion. case report (Maleki & Manley). 57
- Shortened filling period in severe left ventricular disease, diastolic function impairment (Ng & Gibson). 246
- Shunts, intracardiac, Doppler colour flow mapping. case report (Sutherland *et al*) 467
- Smoking and coronary heart disease, reduction of risk after giving up (Robinson *et al*) 16
- Speckle reduction on cross sectional echocardiographic images (Massay *et al*) 298
- Staffing in cardiology, United Kingdom 1988 (Chamberlain *et al*) 482
- Straddling tricuspid valve without ventricular septal defect: case report (Isomatsu *et al*) 222
- Streptokinase
  - to aid drainage of postoperative pericardial effusion: case report (Cross *et al*). 217
  - and heparin treatment, and cardiopulmonary resuscitation, fatal intrathoracic haemorrhage after· case report (Haugeberg *et al*) 157
  - and plasma atrial natriuretic peptide in myocardial infarction: correspondence (Tan *et al*) 238
- Superior QRS axis in ventricular septal defect (Shaw *et al*). 281
- Supravalvar aortic stenosis and peripheral pulmonary artery stenosis in Williams's syndrome (Giddins *et al*). 315
- Supraventricular tachycardia
  - in infants and children, efficacy and safety of adenosine in treatment (Till *et al*). 204
  - paediatric use of flecainide, clinical efficacy and pharmacokinetics (Till *et al*). 133
- Systolic time intervals during first week after myocardial infarction and risk of death during first year (Northover). 429

- Tachycardia
  - atrioventricular nodal reentrant, multiform ventricular tachycardia development during: case report (Bennett & Coyle). 220
  - narrow and broad complex, value and limitations of adenosine in diagnosis and treatment (Rankin *et al*) 195
  - *see also* Supraventricular tachycardia. Ventricular tachycardia

- Tetralogy of Fallot with atrioventricular septal defect, pulmonary artery growth after neonatal balloon dilatation case report (Parsons *et al*) 65
- Thrombosis, intracavitary, in dilated cardiomyopathy detected by cross sectional echocardiography, and systemic emboli, correlation (Ciaccheri *et al*). 26
- Transmitral velocities with heart rate, changes: correspondence (Channer & Jones). 415
- Transposition of the great arteries, right ventricular function 10 years after Mustard operation (Redington *et al*). 455

Transvenous biopsy in antemortem diagnosis of malignant melanoma of right atrium: case report (Gosalakkal & Sugrue). 159
Twins, identical, and hypertrophic cardiomyopathy (Reid *et al*) 384

Ullrich-Noonan syndrome with severe pulmonary hypertension (Tinker *et al*). 74

Valve
  regurgitation, prosthetic, colour flow Doppler mapping in assessment (Chambers *et al*) 1
  semilunar, congenital stenosis, assessment of orifice diameter by multigated pulsed Doppler system, children (de Knecht *et al*) 50
  see also Aortic: Mitral: Pulmonary
Ventricle, ventricular
  fibrillation, intravenous amiodarone in short term treatment (Schutzenberger *et al*). 367
  left, aneurysm, true, after myocardial infarction, and subacute rupture of pseudo aneurysm case report (Goudevenos *et al*) 225
    disease, severe, diastolic function impairment by shortened filling period (Ng & Gibson). 246
    dysfunction, from ischaemic heart disease, effects of xamoterol (Vigholt-Sørensen *et al*) 335
  function, right, influence of respiratory variations (Caplin *et al*). 253
  septal defects, in infants, magnetic resonance imaging at high field strength (Baker *et al*) 305
    multiple, colour flow imaging in diagnosis (Sutherland *et al*) 43
    and superior QRS axis (Shaw *et al*). 281
  septal rupture after myocardial infarction, colour flow mapping value in diagnosis (Smyllie *et al*). 260
    post-infarction, coronary artery disease patterns (Skehan *et al*) 268
  tachycardia, intravenous amiodarone in short term treatment (Schutzenberger *et al*). 367
    recurrent, associated with anomalous left coronary artery from pulmonary artery, revascularisation and map-guided endocardial resection case report (McComb *et al*). 396

White blood cells, changes in flow properties, after myocardial infarction (Nash *et al*). 329
Williams's syndrome, supravalvar aortic stenosis and peripheral pulmonary artery stenosis (Giddins *et al*). 315

Xamoterol, effects on left ventricle dysfunction from ischaemic heart disease (Vigholt-Sørensen *et al*) 335

BRITISH
HEART JOURNAL

Volume 62
1989

BRITISH MEDICAL ASSOCIATION · TAVISTOCK SQUARE · LONDON WC1H 9JR

EDITOR

DENNIS KRIKLER

ASSISTANT EDITORS

M J Davies

Kim Fox

Peter Mills

EDITORIAL COMMITTEE

(Appointed by The British Cardiac Society)

Clive P Aber
Kate Bull
Keith Dawkins
Alan B Houston
Barry R Keeton

Michael Marmot
Alexander L Muir
Paul J Oldershaw
Philip A Poole-Wilson

David B Shaw
Tom Treasure
David E Ward
John Watkins
Peter Wilde

EDITOR, *British Medical Journal*

EDITOR, *Cardiovascular Research*

TECHNICAL EDITOR

Jane Dawson

EDITORIAL ASSISTANT

Anne Oliver

STATISTICAL ADVISER

Stephen J W Evans

CONTENTS OF VOLUME 62

Number 1

COLOUR FLOW DOPPLER MAPPING IN THE ASSESSMENT OF PROSTHETIC VALVE REGURGITATION
J Chambers, M Monaghan, G Jackson 1

AORTIC VALVE REPLACEMENT WITH COMBINED MYOCARDIAL REVASCULARISATION
M Jones, P M Schofield, N H Brooks, J F Dark, H Moussalli, A K Deiraniya, R A M Lawson, A N Rahman 9

WHEN DOES THE RISK OF ACUTE CORONARY HEART DISEASE IN EX-SMOKERS FALL TO THAT IN NON-SMOKERS? A RETROSPECTIVE STUDY OF PATIENTS ADMITTED TO HOSPITAL WITH A FIRST EPISODE OF MYOCARDIAL INFARCTION OR UNSTABLE ANGINA
K Robinson, R M Conroy, R Mulcahy 16

ASSESSING CARDIAC PUMPING CAPABILITY BY EXERCISE TESTING AND INOTROPIC STIMULATION
L B Tan, R J I Bain, W A Littler 20

LACK OF CORRELATION BETWEEN INTRACAVITARY THROMBOSIS DETECTED BY CROSS SECTIONAL ECHOCARDIOGRAPHY AND SYSTEMIC EMBOLI IN PATIENTS WITH DILATED CARDIOMYOPATHY
M Ciaccheri, G Castelli, F Cecchi, M Nannini, G Santoro, V Troiani, A Zuppiroli, A Dolara 26

DIURNAL VARIATION OF PULMONARY ARTERY PRESSURE IN CHRONIC HEART FAILURE
J S R Gibbs, D Cunningham, L M Shapiro, A Park, P A Poole-Wilson, K M Fox 30

INFLUENCE OF NALOXONE ON THE EFFECTS OF HIGH FREQUENCY TRANSCUTANEOUS ELECTRICAL NERVE STIMULATION IN ANGINA PECTORIS INDUCED BY ATRIAL PACING
C Mannheimer, H Emanuelsson, F Waagstein, C Wilhelmsson 36

COLOUR FLOW IMAGING IN THE DIAGNOSIS OF MULTIPLE VENTRICULAR SEPTAL DEFECTS
G R Sutherland, J H Smyllie, B C Ogilvie, B R Keeton 43

ASSESSMENT OF THE ORIFICE DIAMETER BY A MULTIGATED PULSED DOPPLER SYSTEM IN CHILDREN WITH CONGENITAL SEMILUNAR VALVE STENOSIS
S de Knecht, J C W Hopman, O Daniëls, G B A Stoelinga, R S Reneman, A P G Hoeks 50

CASE REPORTS

VENOSPASTIC PHENOMENA OF SAPHENOUS VEIN BYPASS GRAFTS: POSSIBLE CAUSES FOR UNEXPLAINED POSTOPERATIVE RECURRENCE OF ANGINA OR EARLY OR LATE OCCLUSION OF VEIN BYPASS GRAFTS
M Maleki, J C Manley 57

FINDINGS AT NECROPSY IN THE HEART OF A PATIENT WITH ANTICARDIOLIPIN SYNDROME
J J Murphy, I H Leach 61

GROWTH OF THE PULMONARY ARTERY AFTER NEONATAL BALLOON DILATATION OF THE RIGHT VENTRICULAR OUTFLOW TRACT IN AN INFANT WITH THE TETRALOGY OF FALLOT AND ATRIOVENTRICULAR SEPTAL DEFECT
J M Parsons, E J Ladusans, S A Qureshi 65

SUCCESSFUL REPAIR OF AN ATRIAL SEPTAL DEFECT ASSOCIATED WITH RIGHT TO LEFT SHUNTING
K F Hossack, J C Tewksbury, L M Reid 69

SEVERE PULMONARY HYPERTENSION IN ULLRICH-NOONAN SYNDROME
A Tinker, N Uren, J Schofield 74

BOOK REVIEW 78

NOTICES 80

Number 2

CHEMICAL SHIFT MAGNETIC RESONANCE IMAGING OF HUMAN ATHEROMA
R H Mohiaddin, D N Firmin, S R Underwood, A K Abdulla, R H Klipstein, R S O Rees, D B Longmore 81

REGIONAL AORTIC COMPLIANCE STUDIED BY MAGNETIC RESONANCE IMAGING: THE EFFECTS OF AGE, TRAINING, AND CORONARY ARTERY DISEASE
R H Mohiaddin, S R Underwood, H G Bogren, D N Firmin, R H Klipstein, R S O Rees, D B Longmore 90

MAGNETIC RESONANCE IMAGING OF COARCTATION OF THE AORTA IN INFANTS: USE OF A HIGH FIELD STRENGTH
E J Baker, V Ayton, M A Smith, J M Parsons, M N Maisey, E J Ladusans, R H Anderson, M Tynan, A K Yates, P B Deverall 97

PHASE AND AMPLITUDE ANALYSIS OF EXERCISE DIGITAL LEFT VENTRICULOGRAMS IN PATIENTS WITH CORONARY DISEASE J Lyons, M Norell, J Gardener, S Davies, R Balcon, C Layton 102

THE VARIABLE EFFECTS OF ANGIOTENSIN CONVERTING ENZYME INHIBITION ON MYOCARDIAL ISCHAEMIA IN CHRONIC STABLE ANGINA J S R Gibbs, P A Crean, L Mockus, C Wright, G C Sutton, K M Fox 112

DIABETES MELLITUS AS A RISK FACTOR FOR ACUTE MYOCARDIAL INFARCTION IN ASIANS AND EUROPEANS
K L Woods, A Samanta, A C Burden 118

DIASTOLIC FUNCTION AFTER CARDIAC AND HEART-LUNG TRANSPLANTATION
G Hausdorf, N R Banner, A Mitchell, A Khaghani, M Martin, M Yacoub 123

PAEDIATRIC USE OF FLECAINIDE IN SUPRAVENTRICULAR TACHYCARDIA: CLINICAL EFFICACY AND PHARMACOKINETICS
J A Till, E A Shinebourne, E Rowland, D E Ward, R Bhamra, P Haga, A Johnston, D W Holt 133

RESPONSIVENESS OF THE DUCTUS ARTERIOSUS TO PROSTAGLANDIN E_1 ASSESSED BY COMBINED CROSS SECTIONAL AND PULSED DOPPLER ECHOCARDIOGRAPHY
S Hiraishi, N Fujino, K Saito, K Oguchi, N Kadoi, Y Agata, Y Horiguchi, H Hozumi, K Yashiro 140

BALLOON DILATATION OF CONGENITAL AORTIC VALVE STENOSIS IN INFANTS AND CHILDREN: SHORT TERM AND INTERMEDIATE RESULTS M Vogel, L N Benson, P Burrows, J F Smallhorn, R M Freedom 148

CASE REPORTS

POSTPARTUM MYOCARDIAL INFARCTION M A Movsesian, R B Wray 154

FATAL INTRATHORACIC HAEMORRHAGE AFTER CARDIOPULMONARY RESUSCITATION AND TREATMENT WITH STREPTOKINASE AND HEPARIN G Haugeberg, V Bonarjee, K Dickstein 157

MALIGNANT MELANOMA OF THE RIGHT ATRIUM: ANTEMORTEM DIAGNOSIS BY TRANSVENOUS BIOPSY
J A Gosalakkal, D D Sugrue 159

CALCIFIC STENOSIS OF A MITRAL VALVE XENOGRAFT IN A PATIENT IN CHRONIC RENAL FAILURE
M J Raftery, G Koffman, J S Cameron 161

INFECTIVE ENDOCARDITIS IN CROHN'S DISEASE J S K Wong 163

NOTICES 164

Number 3

CARDIAC PARASYMPATHETIC ACTIVITY DURING THE EARLY HOURS OF ACUTE MYOCARDIAL INFARCTION
D McAreavey, J M M Neilson, D J Ewing, D C Russell 165

AORTIC REGURGITATION ASSOCIATED WITH HYPERTROPHIC CARDIOMYOPATHY: A COLOUR DOPPLER ECHOCARDIOGRAPHIC STUDY
T Shiota, T Sakamoto, K Takenaka, K Amano, Y Hada, I Hasegawa, J-I Suzuki, H Takahashi, T Sugimoto 171

CROSS SECTIONAL EARLY MITRAL FLOW VELOCITY PROFILES FROM COLOUR DOPPLER
S O Samstad, H G Torp, D T Linker, O Rossvoll, T Skjaerpe, E Johansen, K Kristoffersen, B A J Angelsen, L Hatle 177

SUBCLINICAL CARDIAC DYSFUNCTION IN ACROMEGALY: EVIDENCE FOR A SPECIFIC DISEASE OF HEART MUSCLE E A Rodrigues, M P Caruana, A Lahiri, J D N Nabarro, H S Jacobs, E B Raftery 185

VALUE AND LIMITATIONS OF ADENOSINE IN THE DIAGNOSIS AND TREATMENT OF NARROW AND BROAD COMPLEX TACHYCARDIAS A C Rankin, K G Oldroyd, E Chong, A P Rae, S M Cobbe 195

EFFICACY AND SAFETY OF ADENOSINE IN THE TREATMENT OF SUPRAVENTRICULAR TACHYCARDIA IN INFANTS AND CHILDREN J Till, E A Shinebourne, M L Rigby, B Clarke, D E Ward, E Rowland 204

VARIABILITY OF THE DOPPLER GRADIENT IN PULMONARY VALVE STENOSIS BEFORE AND AFTER BALLOON DILATATION M K Lim, A B Houston, W B Doig, S Lilley, E P Murtagh 212

CASE REPORTS

USE OF STREPTOKINASE TO AID IN DRAINAGE OF POSTOPERATIVE PERICARDIAL EFFUSION J H Cross, J V De Giovanni, E D Silove 217

DEVELOPMENT OF MULTIFORM VENTRICULAR TACHYCARDIA DURING ATRIOVENTRICULAR NODAL REENTRANT TACHYCARDIA D H Bennett, C Coyle 220

STRADDLING TRICUSPID VALVE WITHOUT A VENTRICULAR SEPTAL DEFECT Y Isomatsu, H Kurosawa, Y Imai 222

SUBACUTE RUPTURE OF A PSEUDOANEURYSM FORMED BY LATE RUPTURE OF A TRUE LEFT VENTRICULAR ANEURYSM J Goudevenos, G Parry, G N Morritt 225

BALLOON DILATATION OF A STENOSED MODIFIED (POLYTETRAFLUOROETHYLENE) BLALOCK-TAUSSIG SHUNT J M Parsons, E J Ladusans, S A Qureshi 228

BRITISH CARDIOLOGY

THE ROOTS OF MODERN BRITISH CARDIOLOGY D M Krikler 230

RELATIONS BETWEEN MEMBERS OF THE BRITISH CARDIAC SOCIETY AND INDUSTRY 235

BOOK REVIEW 236

CORRESPONDENCE 237

NOTICES 240

CORRECTION: IMPACT OF A POLICY OF DIRECT ADMISSION TO A CORONARY CARE UNIT ON USE OF THROMBOLYTIC TREATMENT J M A Burns, K J Hogg, A P Rae, W S Hillis, F G Dunn 240

Number 4

PROTECTIVE EFFECT OF COLLATERAL VESSELS DURING CORONARY ANGIOPLASTY M S Norell, J P Lyons, J E Gardener, C A Layton, R Balcon 241

IMPAIRMENT OF DIASTOLIC FUNCTION BY SHORTENED FILLING PERIOD IN SEVERE LEFT VENTRICULAR DISEASE K S K Ng, D G Gibson 246

INFLUENCE OF RESPIRATORY VARIATIONS ON RIGHT VENTRICULAR FUNCTION J L Caplin, W D Flatman, L Dyke, M N Wiseman, D S Dymond 253

DIAGNOSIS OF VENTRICULAR SEPTAL RUPTURE AFTER MYOCARDIAL INFARCTION: VALUE OF COLOUR FLOW MAPPING J Smyllie, K Dawkins, N Conway, G R Sutherland 260

PATTERNS OF CORONARY ARTERY DISEASE IN POST-INFARCTION VENTRICULAR SEPTAL RUPTURE J D Skehan, C Carey, M S Norell, M de Belder, R Balcon, P G Mills 268

CIGARETTE SMOKING AND NON-FATAL MYOCARDIAL INFARCTION IN WOMEN: IS THE RELATION INDEPENDENT OF CORONARY ARTERY DISEASE? D S Freedman, H W Gruchow, J A Walker, S J Jacobsen, A J Anderson, K A Sobocinski, J J Barboriak 273

SUPERIOR QRS AXIS IN VENTRICULAR SEPTAL DEFECT N J Shaw, M J Godman, A Hayes, G R Sutherland 281

DOPPLER FLOW CHARACTERISTICS IN THE ASSESSMENT OF PULMONARY ARTERY PRESSURE IN DUCTUS ARTERIOSUS
A B Houston, M K Lim, W B Doig, J Gnanapragasam, E N Coleman, M P G Jamieson, J C S Pollock 284

CROSS SECTIONAL ECHOCARDIOGRAPHIC ANATOMY OF COMMON ATRIOVENTRICULAR VALVE IN ATRIAL ISOMERISM
J Arisawa, S Morimoto, J Ikezoe, S Hamada, T Kozuka, T Sano, M Ogawa, H Matsuda, Y Kawashima 291

QUANTITATIVE EFFECTS OF SPECKLE REDUCTION ON CROSS SECTIONAL ECHOCARDIOGRAPHIC IMAGES
R J Massay, R B Logan-Sinclair, J C Bamber, D G Gibson 298

MAGNETIC FRESONANCE IMAGING AT A HIGH FIELD STRENGTH OF VENTRICULAR SEPTAL DEFECTS IN INFANTS
E J Baker, V Ayton, M A Smith, J M Parsons, E J Ladusans, R H Anderson, M N Maisey, M Tynan, N L K Fagg, P B Deverall 305

DILATATION WITH PROGRESSIVELY LARGER BALLOONS FOR SEVERE STENOSIS OF THE PULMONARY VALVE PRESENTING IN THE LATE NEONATAL PERIOD AND EARLY INFANCY
S A Qureshi, E J Ladusans, R P Martin 311

THE NATURAL COURSE OF SUPRAVALVAR AORTIC STENOSIS AND PERIPHERAL PULMONARY ARTERY STENOSIS IN WILLIAMS'S SYNDROME N G Giddins, J P Finley, M A Nanton, D L Roy 315

FAMILY STUDIES OF CONGENITAL HEART BLOCK ASSOCIATED WITH RO ANTIBODY
W M H Behan, P O Behan, J M Reid, W Doig, J Gairns 320

BRITISH CARDIOLOGY
CRISIS IN CARDIOVASCULAR RESEARCH IN BRITAIN M F Oliver 325

NOTICES 328

CORRECTION: RIGHT VENTRICULAR INFARCTION: DIAGNOSTIC ACCURACY OF ELECTROCARDIOGRAPHIC RIGHT CHEST LEADS V3R TO V7R INVESTIGATED PROSPECTIVELY IN 43 CONSECUTIVE FATAL CASES FROM A CORONARY CARE UNIT H R Andersen, E Falk, D Nielsen 328

Number 5

CHANGES IN THE FLOW PROPERTIES OF WHITE BLOOD CELLS AFTER ACUTE MYOCARDIAL INFARCTION
G B Nash, B Christopher, A J R Morris, J A Dormandy 329

EFFECTS OF XAMOTEROL, A β_1 ADRENOCEPTOR PARTIAL AGONIST, IN PATIENTS WITH ISCHAEMIC DYSFUNCTION OF THE LEFT VENTRICLE E Vigholt-Sørensen, O Faergeman, H M Snow 335

THE EPICARDIAL ELECTROGRAM: A QUANTITATIVE ASSESSMENT DURING BALLOON ANGIOPLASTY INCORPORATING MONOPHASIC ACTION POTENTIAL RECORDINGS
P Taggart, P Sutton, R John, R Hayward, H Swanton 342

A STUDY OF NERVES CONTAINING PEPTIDES IN THE PULMONARY VASCULATURE OF HEALTHY INFANTS AND CHILDREN AND OF THOSE WITH PULMONARY HYPERTENSION
K M Allen, J Wharton, J M Polak, S G Haworth 353

TRANSVENOUS ABLATION OF ATRIOVENTRICULAR CONDUCTION WITH A LOW ENERGY POWER SOURCE
E Rowland, D Cunningham, A Ahsan, A Rickards 361

CLINICAL EFFICACY OF INTRAVENOUS AMIODARONE IN THE SHORT TERM TREATMENT OF RECURRENT SUSTAINED VENTRICULAR TACHYCARDIA AND VENTRICULAR FIBRILLATION
W Schützenberger, F Leisch, K Kerschner, W Hárringer, W Herbinger 367

INACCURACIES IN USING AORTIC VALVE GRADIENTS ALONE TO GRADE SEVERITY OF AORTIC STENOSIS
M J Griffith, C Carey, D J Coltart, B S Jenkins, M M Webb-Peploe 372

HLA ANTIGENS IN IDIOPATHIC DILATED CARDIOMYOPATHY C J Limas, C Limas 379

HYPERTROPHIC CARDIOMYOPATHY IN IDENTICAL TWINS J M Reid, A B Houston, E Lundmark 384

ANOMALOUS ORIGIN OF ONE PULMONARY ARTERY FROM THE ASCENDING AORTA: A REVIEW OF ECHOCARDIOGRAPHIC, CATHETER, AND MORPHOLOGICAL FEATURES L V Fong, R H Anderson, R D Siewers, A Trento, S C Park 389

CASE REPORTS

RECURRENT VENTRICULAR TACHYCARDIA ASSOCIATED WITH ANOMALOUS LEFT CORONARY ARTERY FROM THE PULMONARY ARTERY IN A CHILD MANAGED BY REVASCULARISATION AND MAP-GUIDED ENDOCARDIAL RESECTION J M McComb, R Vincent, C J Hilton 396

SUCCESSFUL REPEAT PERCUTANEOUS TRANSLUMINAL CORONARY ANGIOPLASTY AFTER FAILED CORONARY ARTERY SURGERY FOR LEFT MAIN CORONARY ARTERY DISSECTION D R Ramsdale, P M Schofield 400

SPONTANEOUS DISPLACEMENT OF A PACEMAKER ELECTRODE AND ITS SUBSEQUENT SUCCESSFUL REIMPLANTATION J Gialafos, A Theophilis, G Siamas 403

CONGENITAL FISTULA BETWEEN THE LEFT VENTRICLE AND CORONARY SINUS: ELUCIDATION BY COLOUR DOPPLER FLOW MAPPING J P Gnanapragasam, A B Houston, S Lilley 406

HEART TRANSPLANTATION FOR CHURG-STRAUSS SYNDROME D Thomson, H Chamsi-Pasha, P Hasleton 409

BRITISH CARDIOLOGY

THE RANDOMISED INTERVENTION TREATMENT OF ANGINA (RITA) TRIAL PROTOCOL: A LONG TERM STUDY OF CORONARY ANGIOPLASTY AND CORONARY ARTERY BYPASS SURGERY IN PATIENTS WITH ANGINA R A Henderson 411

CORRESPONDENCE 415

NOTICES 416

Number 6

INTEGRATION OF AMBULANCE STAFF TRAINED IN CARDIOPULMONARY RESUSCITATION WITH A MEDICAL TEAM PROVIDING PREHOSPITAL CORONARY CARE W A McCrea, E Hunter, C Wilson 417

HAEMORRHEOLOGICAL ABNORMALITIES IN UNSTABLE ANGINA PECTORIS: A RELATION INDEPENDENT OF RISK FACTOR PROFILE AND ANGIOGRAPHIC SEVERITY F-J Neumann, H Tillmanns, P Roebruck, R Zimmermann, H-M Haupt, W Kübler 421

ESTIMATION OF THE RISK OF DEATH DURING THE FIRST YEAR AFTER ACUTE MYOCARDIAL INFARCTION FROM SYSTOLIC TIME INTERVALS DURING THE FIRST WEEK B J Northover 429

A COMPARISON OF METHODS OF ANALYSING EXERCISE TESTS FOR DIAGNOSIS OF CORONARY ARTERY DISEASE J W Deckers, B J Rensing, J G P Tijssen, R V H Vinke, A J Azar, M L Simoons 438

PHYSIOLOGICAL HYPERTROPHY OF THE HEART AND ATRIAL NATRIURETIC PEPTIDE DURING REST AND EXERCISE J Svanegaard, K Angelo-Nielsen, J S Hansen 445

CLINICAL COURSE OF ENDOMYOCARDIAL FIBROSIS P N Gupta, M S Valiathan, K G Balakrishnan, C C Kartha, M L Ghosh 450

RIGHT VENTRICULAR FUNCTION 10 YEARS AFTER THE MUSTARD OPERATION FOR TRANSPOSITION OF THE GREAT ARTERIES: ANALYSIS OF SIZE, SHAPE, AND WALL MOTION A N Redington, M L Rigby, P Oldershaw, D G Gibson, E A Shinebourne 455

CARDIAC INVOLVEMENT IN CHURG-STRAUSS SYNDROME SHOWN BY ECHOCARDIOGRAPHY J M Morgan, L Raposo, D G Gibson 462

CASE REPORTS

POTENTIAL VALUE OF INTRAOPERATIVE DOPPLER COLOUR FLOW MAPPING IN OPERATIONS FOR COMPLEX INTRACARDIAC SHUNTING G R Sutherland, S Balaji, J L Monro 467

UNUSUAL AND INTRAOPERATIVE EPICARDIAL ECHOCARDIOGRAPHIC FEATURES OF A PAPILLARY TUMOUR OF THE AORTIC VALVE N P Lewis, G T Williams, A G Fraser 470

SEVERE HAEMOLYTIC ANAEMIA AFTER REPLACEMENT OF THE MITRAL VALVE BY A ST JUDE MEDICAL PROSTHESIS H Feld, J Roth 475

HYPOPLASTIC RIGHT RETRO-OESOPHAGEAL AORTIC ARCH: SIMILARITIES TO INTERRUPTED AORTIC ARCH W B Knight 477

BRITISH CARDIOLOGY

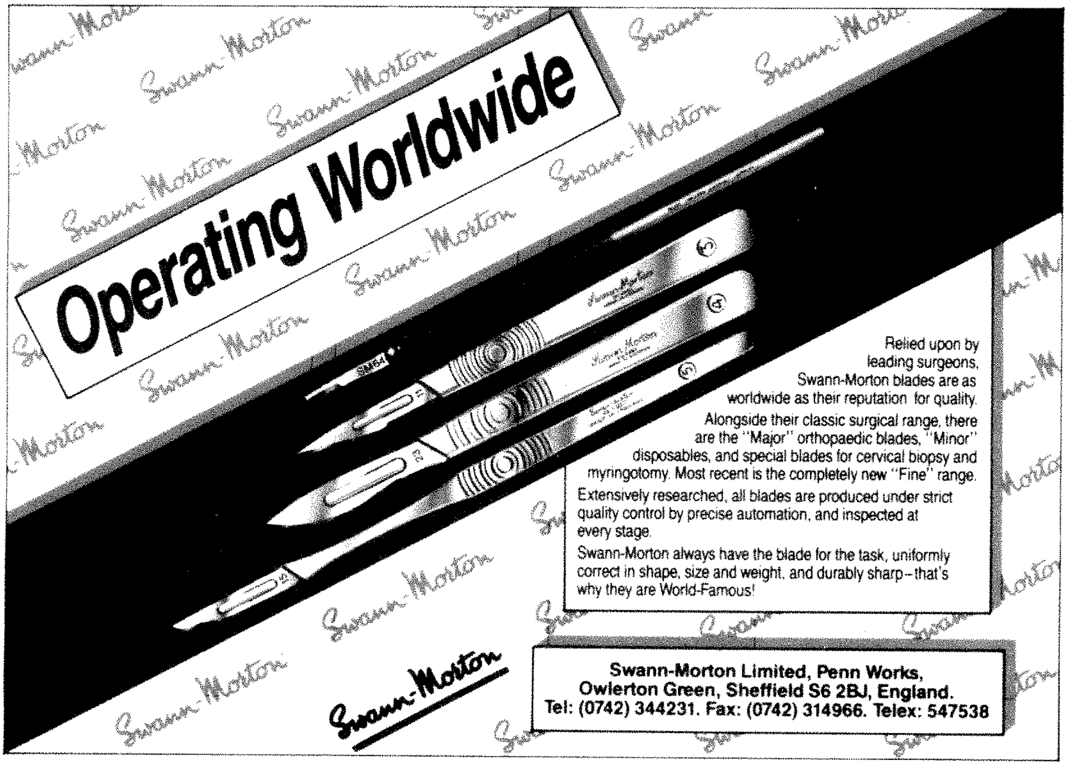
STAFFING IN CARDIOLOGY IN THE UNITED KINGDOM 1988: FIFTH BIENNIAL SURVEY D Chamberlain, L Bailey, E Sowton, D Ballantyne, D McC Boyle, M Oliver 482

BOOK REVIEW 488

CORRESPONDENCE 489

NOTICES 492

INDEX 493

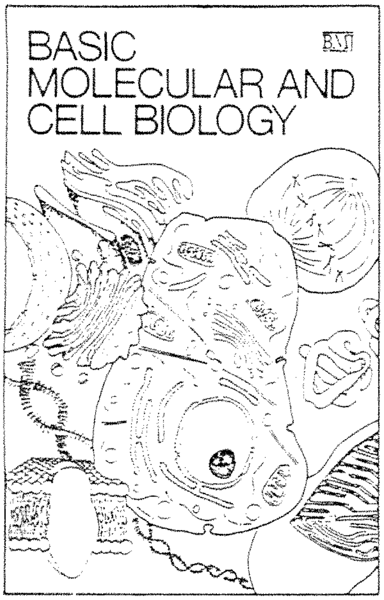


Relied upon by leading surgeons, Swann-Morton blades are as worldwide as their reputation for quality. Alongside their classic surgical range, there are the "Major" orthopaedic blades, "Minor" disposables, and special blades for cervical biopsy and myringotomy. Most recent is the completely new "Fine" range.

Extensively researched, all blades are produced under strict quality control by precise automation, and inspected at every stage.

Swann-Morton always have the blade for the task, uniformly correct in shape, size and weight, and durably sharp – that's why they are World-Famous!

Swann-Morton Limited, Penn Works,
Owlerton Green, Sheffield S6 2BJ, England.
Tel: (0742) 344231. Fax: (0742) 314966. Telex: 547538



The extraordinary technical developments in molecular biology over the past few years, and the equally rapid advances in understanding of cell biology, will almost certainly result in far reaching changes in medical research and practice. In this collection of articles experts in molecular and cell biology provide the background information to give clinicians an insight into the way in which the medical sciences may be moving over the next few years and into the exciting possibilities opening up for the treatment of genetic disorders, cancer, and the common illnesses of Western society such as degenerative vascular disease and diabetes.

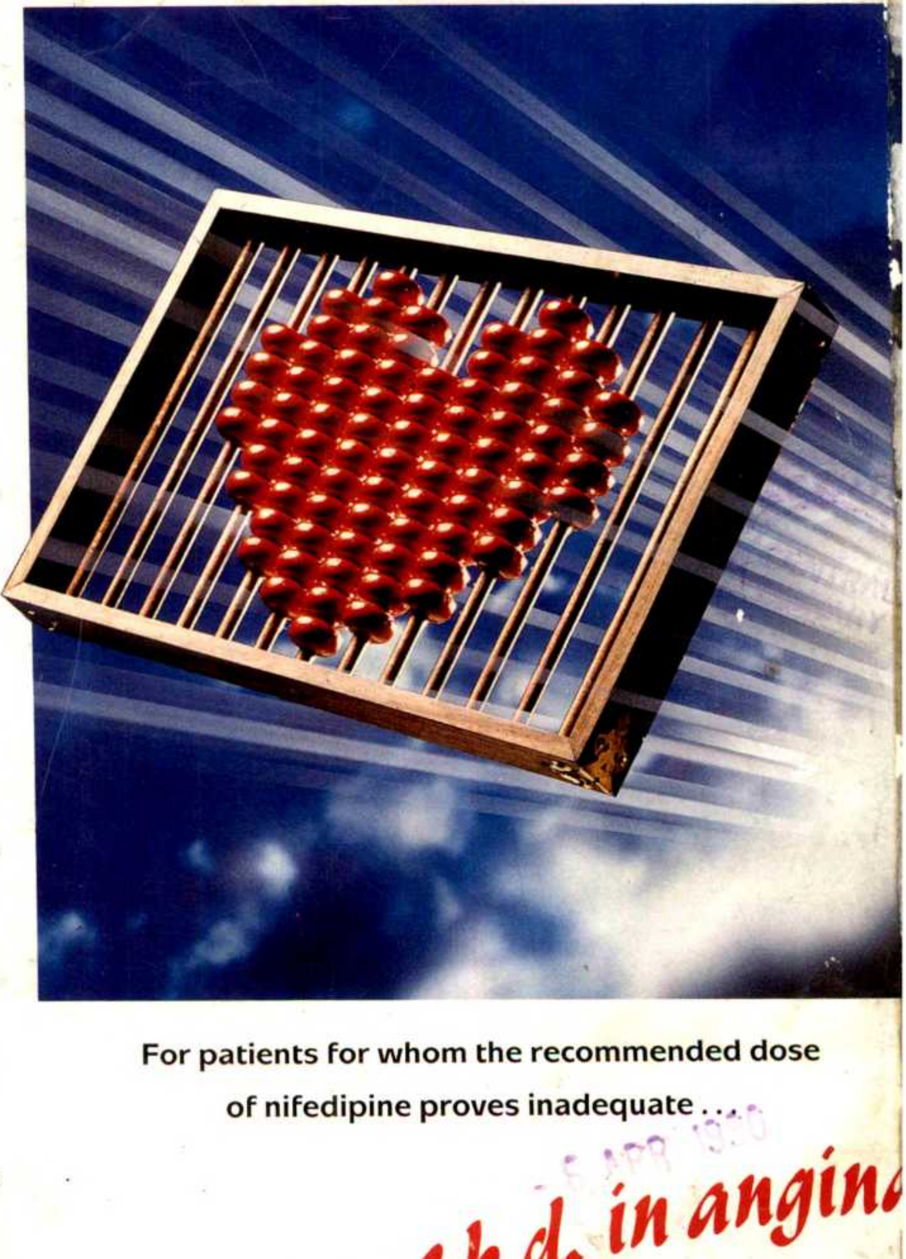
Price: Inland £5.95; Abroad £7.50
BMA members: Inland £5.45; Abroad £7.00
including postage, by air abroad.
Payment must be enclosed with order.

Order from BRITISH MEDICAL JOURNAL, PO Box 295, London WC1H 9TE
or any leading medical bookseller

Published by British Medical Association, Tavistock Square, London WC1H 9JR

Tenif

Try counting on 'Tenif' for effective angina control



ESCRIBING NOTES FOR 'TENIF'
ESENTATION
ng atenolol +20mg nifedipine.

SAGE

NAGEMENT OF HYPERTENSION – illy one capsule daily; recommended ere therapy with either a calcium channel cker or a beta-blocker proves inadequate. ecessary one capsule twice dally.

NAGEMENT OF ANGINA – One capsule ce daily, recommended where therapy with ner a calcium channel blocker or beta-cker proves inadequate.

ILDREN – Not recommended.

DERLY PATIENTS – Dosage should not eed one capsule daily in hypertension or e capsule twice daily in angina.

NTRA-INDICATIONS

art block, cardiogenic shock, overt heart lure, women of childbearing potential, tation. Co-administration with diodepressants e.g. verapamil.

ECAUTIONS

treated cardiac failure, bradycardia, aesthesia. Caution in patients with chronic structive airways disease or asthma. thdrawal of beta-blocking drugs should be adual in patients with ischaemic heart ease. Withdrawal of clonidine. Co-ministration with Class I antidysrhythmic ents. Interactions with cimetidine or inidine.

abetes: Diabetic patients receiving 'Tenif' ay require adjustment of their diabetic erapy. Modification of the tachycardia of poglycaemia may occur.

epatic or renal impairment: In patients with arked renal impairment (i.e. creatinine earance below 15ml/min/1.73m^2, serum eatinine greater than 600 micromol/litre) e use of 'Tenif' is considered inappropriate. re should be taken in patients with marked epatic impairment.

DE EFFECTS

eadache, flushing, fatigue, dizziness and edema may occur. Skin rashes and dry eyes ve been reported with beta-blockers – nsider discontinuance if they occur. are reports of jaundice and gingival perplasia with nifedipine.

RODUCT LICENCE NUMBERS AND BASIC HS COST:

enif' Capsules 29/0202, 29/0216 calendar packs of 28, £10.90.

data sheet is available and should be onsulted before prescribing.

enif' is a trade mark.

urther information is available on request om the Company.

STUART

Stuart Pharmaceuticals Limited
Stuart House, 50 Alderley Road
Wilmslow, Cheshire SK9 1RE

For patients for whom the recommended dose of nifedipine proves inadequate . . .

1 b.d. in angina

Tenif

atenolol 50mg, nifedipine 20 mg

F IN ANGINA TENIF IN ANGINA TENIF IN ANGINA TENIF IN ANGINA TENIF IN ANGINA TEN